Bias from historical control groups used in orthodontic research: a meta-epidemiological study

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Abstract: AIM The validity of meta-analysis is dependent upon the quality of included studies. Here, we investigated whether the design of untreated control groups (i.e. source and timing of data collection) influences the results of clinical trials in orthodontic research. MATERIALS AND METHODS This meta-epidemiological study used unrestricted literature searching for meta-analyses in orthodontics including clinical trials with untreated control groups. Differences in standardized mean differences (ΔSMD) and their 95% confidence intervals (CIs) were calculated according to the untreated control group through multivariable random-effects meta-regression controlling for nature of the interventional group and study sample size. Effects were pooled with random-effects synthesis, followed by mixed-effect subgroup and sensitivity analyses. RESULTS Studies with historical control groups reported deflated treatment effects compared to studies with concurrent control groups (13 meta-analyses; ΔSMD = -0.31; 95% CI = -0.53, -0.10; P = 0.004). Significant differences were found according to the type of historical control group (based either on growth study or clinical archive; 11 meta-analyses; ΔSMD = 0.40; 95% CI = 0.21, 0.59; P < 0.001). CONCLUSIONS The use of historical control groups in orthodontic clinical research was associated with deflation of treatment effects, which was independent from whether the interventional group was prospective or retrospective and from the study's sample size. Caution is warranted when interpreting clinical studies with historical untreated control groups or when interpreting systematic reviews that include such studies.

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Title Page

Bias from historical control groups used in orthodontic research: a meta-epidemiological study

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Summary

Aim: The validity of meta-analysis is dependent upon the quality of included studies. Here, we investigated whether the design of untreated control groups (i.e. source and timing of data collection) in orthodontic research influences the results of clinical trials.

Materials and methods: This meta-epidemiological study used unrestricted literature searching for meta-analyses in orthodontics with clinical trials with untreated control groups. Differences in standardized mean differences (ΔSMD) and their 95% confidence intervals (CIs) were calculated according to the untreated control group through multivariable random-effects meta-regression controlling for nature of the interventional group and study sample size. Effects were pooled with random-effects synthesis, followed by mixed-effect subgroup and sensitivity analyses.

Results: Studies with historical control groups reported deflated treatment effects compared to studies with concurrent control groups (13 meta-analyses; ΔSMD=-0.31; 95% CI=-0.53,-0.10; P=0.004). Finally, significant differences were found according to the type of historical control group (based either on growth study or clinical archive; 11 meta-analyses; ΔSMD=0.40; 95% CI=0.21,0.59; P<0.001).

Conclusions: The use of historical control groups in orthodontic clinical research was associated with deflation of treatment effects, which was independent from whether the interventional group was prospective or retrospective and from the study's sample size. Caution is warranted when interpreting clinical studies with historical untreated control groups or when interpreting systematic reviews that included such studies.

Registration: PROSPERO (CRD42015024179)

Conflict of interest: None

Main Text

Introduction

Rationale

Meta-analysis of clinical trials provides the best evidence for evaluating orthodontic interventions, due to the increased statistical power and precision (1). However, if the methodological quality of these studies is suboptimal, then the results will be biased, even if the meta-analysis is conducted to the highest standards (2). Ideally, meta-analyses assessing the comparative effectiveness of orthodontic interventions would include only well-conducted clinical trials, and especially randomized controlled trials (RCTs), which are seen as the epitome of clinical research (2).

However, high quality clinical trials do not always exist or are simply not always feasible and non-randomized controlled trials of interventions (non-RCTs) are often included in systematic reviews and meta-analyses in orthodontics (3-5), which can potentially affect their conclusions. Currently, clinical trials in the orthodontic literature consist of only a modest proportion of RCTs, where patients are randomly allocated to an intervention or a control group, whilst the rest are non-RCTs (3,6).

As far as intervention groups are concerned, these can consist either of patients allocated to a prospective interventional group or can consist of files from already-treated patients collected to form a retrospective interventional group. Historically, a large proportion of evidence concerning the performance of an orthodontic intervention has stemmed from retrospective studies (5,7), although the contribution of prospective studies has increased in the last decades (3,8).

The use of control groups in research has one major purpose: to allow discrimination of patient outcomes (for example, changes in symptoms, signs, or other morbidity) caused by the test treatment from outcomes caused by other factors, such as the natural progression of the disease, observer or patient expectations, or natural growth. As far as control groups are concerned, untreated control groups have been extensively used in a large number of orthodontic clinical investigations (7,8). In an ideal clinical setting, patients are randomly allocated to either an active intervention group or to a concurrent untreated control group, where patients are followed parallel to the intervention group. Although untreated control groups enable more accurate estimation of the therapeutic effects by ruling out natural processes (like growth), they are not without problems. The principal difficulties with untreated control groups are that the patients must be followed longitudinally and additional diagnostics need to be collected at various timepoints, including radiographs, which can be problematic to justify (9). In this sense, and taking into account the problem of radiation exposure to untreated children, orthodontic researchers have attempted to make use of existing cohorts of untreated patients that have been already been collected in the last half century to inform clinical trials. Data for such historical control groups might be collected from either routinely-collected clinical archives from orthodontic university clinics, private practices or large-scale community longitudinal growth studies. The main concerns with historical control groups are imbalance in distribution of patient characteristics, selection bias, and temporal bias. Additionally, the outcomes of such trials pertain mainly to cephalometrics and cast model analysis, which might not reflect contemporary patient perspectives (10).

Empirical evidence relating to the effect of study design characteristics on treatment effects can be derived from meta-epidemiologic studies that integrate data from a collection of meta-analyses (11). In this collection of meta-analyses, all primary studies (here termed “component trials”) are classified according to a specific study-level characteristic and then synthesized. As an example, it has been shown that inadequacies in the generation of a randomization sequence, allocation concealment or blinding in RCTs can lead to biased estimates (12). Concerning research in orthodontics, empirical evidence has shown that the design of clinical trials systematically influences the magnitude and direction of the results, with non-RCTs, and especially retrospective ones, overestimating treatment effects (7).

Objectives

The primary aim of this meta-epidemiological study was to identify the extent of inconsistent results between orthodontic trials with concurrent control groups and trials with historical control groups. Secondarily, we aimed to assess existing differences in the study results between studies with various forms of HCtrs.

Methods

Protocol and registration

In this report we adopt previously-defined terminology (7) and define as ‘systematic review’ a structured review with *a priori* planned procedures of study identification, study selection, data extraction and quality assessment. We define ‘meta-analysis’ as the procedure of statistical synthesis of the results of two or more studies. Primary studies (here, clinical trials) included in a systematic review or a meta-analysis are termed ‘component trials’. Finally, the pooling of multiple meta-analyses according to a specific factor (for example, study design) is termed ‘meta-epidemiological synthesis’.

As far as intervention groups are concerned, they could be either (1) prospective or (2) retrospective. As far as untreated control groups are concerned, we categorize them as follows: (1) concurrent control group: patients allocated prospectively in an untreated control group, which is actively observed parallel to the interventional group, and (2) historical control group: control group formed from patient data already collected prior to the initiation of the study. Sources for historical control data could be either orthodontic longitudinal growth studies or clinical patient archival records (either from the same source as the interventional group or from a different source).

The protocol for this study was registered prospectively in PROSPERO (CRD42015024179) before study initiation.

Eligibility criteria

Eligible for this study were systematic reviews in orthodontics with at least one meta-analysis of interventional studies with untreated control group(s). As a requirement, either the raw data or the calculated Standardized Mean Difference (SMD) should be reported in the published report. No limitations concerning language, publication year or publication type were adopted.

Information sources and literature search

Study selection was based on previously published meta-epidemiological databases (7, 13), while systematic reviews were also identified by searching five literature databases from inception to July 2015 without any language, publication year or publication status restriction (Supplementary Table 1). Manual searches were performed in MEDLINE, Google, and Google scholar up to August 2015 for additional clinical trials. Finally, the search was updated in MEDLINE in March 2016 prior to publication.

Study selection

The titles of all obtained reports were screened by two authors (S.N.P., V.K.). Subsequently, after acquiring the full-text of all possibly eligible systematic reviews, the same two authors (S.N.P., V.K.) applied independently the eligibility criteria to their abstracts and, if needed, to their full-text, while a third author resolved conflicts (A.J.).

Data collection

A pre-defined form was used to extract the characteristics of included systematic review by one author (S.N.P.), while a second author (V.K.) checked all data by reading again the systematic review report. Extracted data included the review's Pubmed unique Identifier, subject, and number of performed meta-analyses. All meta-analyses from the included systematic reviews were extracted and data was collected including: subject, intervention, number of trials, and raw study-level data (when available). When these data were not provided, we read the full-text of the trials and extracted them. Multiple meta-analyses were extracted from a systematic review only when the component trials or their outcomes differed. Subgroup analyses were ignored, if an overall pooled estimate of the subgroups was given. When the subgroups were not pooled together, data were extracted from the largest subgroup.

Regarding the included component studies, MEDLINE was searched through PubMed in order to assign a Pubmed unique identifier to each one of them. Trials not indexed in MEDLINE were manually assigned a unique identifier and the full-text of all included trials was acquired. To remove trial overlaps among reviews, we merged similar meta-analyses from different reviews and also added any manually-identified additional trials. Data collected at the component trial level included the design of each included component trial, the enrollment/allocation source of the patients in the experimental (interventional) group(s), and the untreated control group. Data extraction and characterization of study design was performed independently by two authors (S.N.P., V.K.) based on the full-text of each review/component trial, as misclassification of study designs in the orthodontic literature has been reported. In one instance, where no final judgment about trial design could be made, the trial was omitted. A preliminary calibration between the two authors responsible for extraction (S.N.P., V.K.) was conducted prior to the actual extraction procedures until perfect consensus was reached.

Data synthesis

Calculating effects within each meta-analysis

For all included meta-analyses, the SMD was chosen as the effect measure because it standardizes estimates by their variability and enables overall synthesis (14). After the initial construction of the meta-epidemiological database, it became apparent that numerous secondary cephalometric outcomes were included, and objective judgments about their beneficial/detrimental direction were not possible, which precluded expressing all meta-analyses on universal direction. It was decided *post hoc*, therefore, to include from each systematic review only the main outcomes that included the largest number of studies and pertained directly to the problem addressed.

All SMDs were recoded on the same direction, so that a positive SMD was beneficial. When trials with more than one experimental (interventional) trial arms were included, these arms were pooled prior to the meta-analysis to avoid double-counting of control patients.

Random-effects meta-regression was performed, fully incorporating heterogeneity between-trials, to derive a 'difference in SMDs' (ΔSMD) and the standard error for each meta-analysis, according to the design of the untreated control group. An iterative residual maximum likelihood algorithm was used for the estimation of between-study variance, due to its performance (15), and the Knapp-Hartung modification (16) was used for the calculation of the ΔSMDs, which accounts for the uncertainty in the heterogeneity estimate (17). The magnitude for SMDs and ΔSMD was assessed with the following guidelines (0.2 = small effect; 0.5 = medium effect; 0.8 = large effect) (14). These cut-off values were arbitrarily adopted to visually enhance the produced forest plots.

Two statistical comparisons were conducted: (1) concurrent or historical control groups, and (2) historical control groups based on growth studies or on clinical patient archival records. Supported by existing empirical evidence (7, 13), all analyses were adjusted via multivariable meta-regression for the nature of the interventional group (prospective/retrospective) and differences in the sample size among trials. The effects of these confounders were noted, but are not discussed in detail, as they fall outside the scope of this study.

Meta-epidemiological synthesis among meta-analyses

The ΔSMDs among meta-analyses were pooled with the *metan* macro (random-effects model based on the DerSimonian and Laird method). Between-meta-analysis heterogeneity was assessed with the heterogeneity parameter τ^2, whilst between-meta-analysis inconsistency was quantified with the I^2 statistic, defined as the proportion of total variability in the results explained by heterogeneity (18). The 95% uncertainty intervals (similar to CIs) around the I^2 were calculated using the non-central χ^2 approximation of Q. 95% predictive intervals were calculated for the ΔSMD, which incorporate existing heterogeneity and provide a range of possible effects for a future meta-analysis (19). All analyses were run in Stata SE 13.0 (StataCorp, College Station, TX). A two-tailed P-value of 0.05 was considered significant for hypothesis-testing, except for a 0.10 used for the test of heterogeneity and reporting biases (20).

Additional analyses

Mixed-effect subgroup analyses were performed to identify possible differences of control group role according to the various fields of orthodontics. Additional subgroup analyses were planned, but could not be performed due to limited data (see protocol). Indications of reporting biases (including small-study effects) were assessed with Egger's linear regression test and contour-enhanced funnel plots, if 10 or more meta-analyses were included in a meta-epidemiological synthesis.

Sensitivity analyses

Sensitivity analyses were performed by (1) comparing the results of fixed-effect and random-effects models (as no strict guidelines exist regarding model use in meta-epidemiological studies); (2) including one meta-analysis per systematic review; (3) including only the largest meta-analysis from each comparison; and (4) including only the most precise 50% from the number of eligible meta-analyses (i.e. having the lowest standard error) for each comparison. Supplementary Figure 1 gives an overview of the study's procedures.

Results

Study selection

Following an initial screening of the pre-existing database and manual literature update, a total of 294 relevant systematic reviews were identified (Figure 1). A total of 280 systematic reviews were excluded after consideration (Supplementary Table 2), leaving 14 relevant reviews (Supplementary Table 3) with 122 meta-analyses for inclusion. After the addition of manually-identified 12 trials and the merging of similar meta-analyses to remove overlaps, a total of 65 meta-analyses with 132 unique component trials (493 trials with overlap) were included.

Study characteristics

A total of 132 unique component trials were identified from the electronic and manual search, while 10 of them were excluded for having no untreated control group (Figure1), leaving 122 trials. The overview of these trials is provided in Table 1 and the nature of the experimental and control groups are provided in detail in Supplementary Table 4. Patients were allocated to a prospective intervention group in 58% of the trials (25% random allocation – 33% non-random allocation), while patients were allocated prospectively to a concurrent control group in 39% of the trials. On the other hand, historical control groups were used in 62% of the included trials. This means that there were also prospective clinical trials were patients were actively allocated to an intervention group, while the untreated control group consisted of existing (retrospective) patient data. The historical control groups consisted of growth studies in 28% of the cases and clinical archives in 34% of the cases (28% from the same and 6% from another source as the interventional group). A total of 31 trials included a growth study control, with the most used growth study being the Michigan study (n=24), and the Denver study (n=9), and the Bolton-Brush study (n=4) (Supplementary Table 5).

Results of individual studies and data synthesis

Historical versus concurrent controls

After excluding meta-analyses of secondary outcomes that could not be objectively classified as beneficial or detrimental (Supplementary Table 6), a total of 28 meta-analyses were considered eligible. From these, 13 meta-analyses with 171 trials and 9805 patients included both historical and concurrent control groups and could be pooled, while adjusting for having nature of interventional group (prospective/retrospective) and sample size. On average, trials with historical control showed smaller treatment effects compared to trials with concurrent controls (adjusted ΔSMD = -0.31; 95% CI = -0.53 to -0.10; P = 0.004; Table 2 and Figure 2).

Historical controls type

A total of 11 meta-analyses with 108 trials and 6439 patients included historical controls from both growth studies and clinical archives and could be pooled. On average, trials with historical controls from growth studies showed larger treatment effects compared to trials with historical controls from clinical archives (adjusted ΔSMD = 0.40; 95% CI = 0.21 to 0.59; P < 0.001; Table 2 and Figure 3).

Additional analyses

According to the subgroup analyses (Table 3), no difference was found among the identified orthodontic fields for the comparison of historical versus concurrent controls (P among subgroups = 0.867). Likewise, no indications of reporting bias and small-study effects among meta-analyses could be found with Egger's test (intercept = -0.49; 95% CI = -1.14 to 0.16; P = 0.129) or through inspection of the funnel plots (Supplementary Figure 2).

On the other hand, considerable variation of ΔSMDs was found among the various orthodontic fields for the comparison of growth study versus clinical archive historical controls, although no significant difference was found (P among subgroups = 0.400). Finally, indications of reporting bias and small-study effects among meta-analyses could be found with Egger's test (intercept = -0.53; 95% CI = -1.10 to 0.05; P = 0.069) and through inspection of the funnel plots (Supplementary Figure 2), although these were not statistically significant.

Sensitivity analyses

For both meta-epidemiological comparisons the results of the sensitivity analyses were similar to the original analyses (Table 3), with consistent direction, but hampered precision following reduction in the sample size.

Discussion

Summary of evidence

As far as we are aware, this is the first empirical study to assess the influence of the control group's nature on the results of orthodontic clinical trials. Despite the relatively restricted sample of included meta-analyses, the design of the control group influenced the meta-analysis results, independently of the design of the intervention group.

Based on the empirical evidence, the results from trials with concurrent controls differed from trials with historical controls (Table 2). Moreover, as multivariable meta-regression was used, this difference was irrespective of the nature of the experimental group (whether this was prospective or retrospective) and the trial's sample size. This could be interpreted as an un-confounded sign of bias directly originating from the nature of the control group. Historical controls in orthodontics are used more often (12%) (8) compared to other disciplines, like plastic and reconstructive surgery (3%) (21). In one of the earliest assessments of the control group's design, Sacks *et al*. (22) compared the results of RCTs and HCtr trials in six fields including cirrhosis, coronary surgery, myocardial infarction, cancer, and habitual abortion. They found that the overall probability of a treatment to be proven effective by a trial with historical control was increased by 293%-383% compared to RCTs, even when the former were matched/adjusted for known prognostic factors. Additionally, the probability of a trial with historical control reporting a significant treatment outcome ($P < 0.05$) was increased by 181% compared to RCTs. Possible explanation for these discrepancies might be bias originating from the control group design or increased risk of publication bias (22). This is also in agreement with recent empirical evidence indicating that non-RCTs are associated with excess statistical significance (23). Additionally, secular trends have been reported to exist in the widely-used orthodontic growth studies, with different birth cohorts having distinctive growth patterns (24). Overall, the use of historical controls seems to be associated with systematic bias, independently of the intervention group and should therefore be avoided, if possible. Altman and Bland

(25) likewise suggested that the use of historical controls can be justified only in tightly controlled situations of relatively rare conditions, such as in evaluating treatments for advanced cancer (26).

Additionally, the results from trials with growth study historical controls differed from trials with clinical archive historical controls (Table 2). This might indicate that different extent of bias might be attributed to the various types of historical control groups. Subgroup analysis indicated that differences existed between the two types of historical controls in trials of Class II malocclusion and transverse deficiencies. Subgroup and sensitivity analysis indicated that differences might exist according the various orthodontic fields (ΔSMDs of 0.40 and -0.81 for Class II and Class III treatment, respectively), while possible signs of small study effects were also seen, although both were not statistically significant. In any case, due to the small number of contributing meta-analysis and the contradicting effect directions, the credibility of these subgroups is low.

Ethical considerations should also be taken into account, when choosing the appropriate control group. When a therapy is intended to treat a serious illness for which there is no satisfactory standard-of-care, especially if this new therapy is seen as promising on the basis of theoretical considerations, animal data, or early human experience, there may be understandable reluctance to perform a comparative study with a concurrent control group of patients who would not receive the new treatment. At the same time however, it is not responsible or ethical to carry out studies that have no realistic chance of credibly showing the actual efficacy of the treatment (27). Alternatively, and generally preferably, even the earliest trials for a new treatment could be randomized and carefully monitored by independent sources for early signs of clear benefit. Trials with concurrent control groups can detect extreme effects very rapidly and, in addition, can detect modest, but still valuable, effects that would not be credibly demonstrated by trial with a historical control group (27).

Although this was not the primary scope of this study, empirical evidence indicated that retrospective trials are associated with inflated treatment effects compared to prospective trials (Supplementary Table 7). This can be interpreted as bias originating from retrospective trial design, which is also independent of the nature of the control group (whether this is concurrent or historical). Additionally, the extent of bias of retrospective trials identified from this study is larger than previous evidence (ΔSMD of -0.49 compared to an ΔSMD of -0.30 from a previous study (7)). This might be attributed to the different sample of meta-analyses used by the two studies, as only meta-analyses with untreated controls were included in this study. Alternatively, this might be attributed to the fact that multivariable meta-regression was applied in this study, to factor out the confounding effect of the control group design. A tendency for RCTs to agree more with prospective compared to retrospective non-RCTs has been described (28). This can be explained by the fact that retrospective trial are more prone to selection bias, observation bias, and confounding by indication than prospective trials. It is also possible that many retrospective trials are conducted using data that have been collected for other purposes and therefore may not be as complete or unbiased as one would wish (29).

When incorporating non-randomized clinical trials in systematic reviews, it will always make sense to explore potential sources of heterogeneity as well as adopt a random-effects approach to acknowledge the unexplained heterogeneity (30, 31). Various methods have also been suggested to inform the meta-analysis results about the extent of bias by empirically based priors (32) or directly by mixed treatment comparison meta-analysis (33), but are not widely used and may require specialized statistical expertise and software (34).

Strengths and limitations

The strengths of this study include the extensive literature search, which was not restricted to orthodontic journals and the *a priori* registration with transparent reporting of all *post hoc* changes (Supplement). Also, misclassification of component trials was minimized, as the full texts of every component trial in the meta-analyses were acquired and assessed first-hand. Furthermore, the calculations of ΔSMDs took into account the heterogeneity between studies in each meta-analysis, while the heterogeneity did not pose a great problem for the meta-epidemiological synthesis (35). The magnitude of the control groups influence small to medium, meaning that the observed differences could possibly have a bearing on the clinical decision regarding this treatment. Finally, the results of the meta-epidemiological analyses for both comparisons were rather robust, as seen from the sensitivity analyses.

There are also some limitations to this study. Due to the inclusion criteria of this empirical assessment, only a subsample of existing meta-analyses could be included. For example, meta-analyses including only one type of control group were excluded, limiting the final sample of eligible meta-analyses. As with all epidemiological studies, various interventions and various outcomes were pooled together, allow with was facilitated appropriately with the SMD. Additionally, as the SMD was used as effect measure, the results of the meta-analyses are dependent on the observed variation across studies. *Post hoc* power calculation (36) indicated that a total of at least 17-20 meta-analyses would be needed to achieve an 80% power for the comparison of historical versus concurrent controls. This indicates that the statistical power of the present study could be improved by the addition of more meta-analyses. As however the effect of historical controls was consistent in all included meta-analyses, the overall effect was statistically significant, and no asymmetry was seen in the funnel plot, low power doesn’t pose a threat to the results’ credibility. Additionally, some variation in the observed results might be due to inadequate matching between intervention and historical control groups, although it is expected that authors of such studies have carefully planned this aspect of their study. Finally, the use of design labels for trial groups as ‘prospective’ and ’retrospective‘ is ambiguous and, based on personal judgment of the authors, might not always reflect the truth.

Conclusions

Existing evidence from orthodontic meta-analyses indicates that there exist systematic differences between trials with concurrent untreated controls and trials with historical untreated controls. Additionally, these differences are independent from previously-identified differences between trials with prospective intervention or retrospective intervention groups. Finally, no consistent difference could be found between historical control groups from growth studies and historical control groups from clinical archives, although imprecision and small-study effects for this comparison cannot be ruled out.

Implications for future research

- Clear reporting of both experimental and control groups, preferably in the title or abstract, is suggested.
- For clinical questions where comparisons with untreated controls are needed, systematic reviews should preferably include studies with concurrent untreated controls.
- In case untreated concurrent controls might be judged unethical, these can be substituted by active control groups, where patients receive a standard-of-care therapy.
- If no such trials are available or if authors decide to also include studies with historical controls, the authors could perform sensitivity analyses to check the robustness of the results.
- Conclusions from systematic reviews based solely on trials with historical control groups, and especially trials with retrospective interventional groups and historical control groups, should be viewed with caution.

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35. Papageorgiou, S.N. (2014) Meta-analysis for orthodontists: Part II--Is all that glitters gold? *Journal of Orthodontics*, 41, 327–36.

36. Giraudeau, B., Higgins, J.P., Tavernier, E. and Trinquart, L. (2016) Sample size calculation for meta-epidemiological studies. *Statistics in Medicine*, 35, 239–50.

Figure legends

Figure 1. Flowdiagram for the identification and selection of studies.

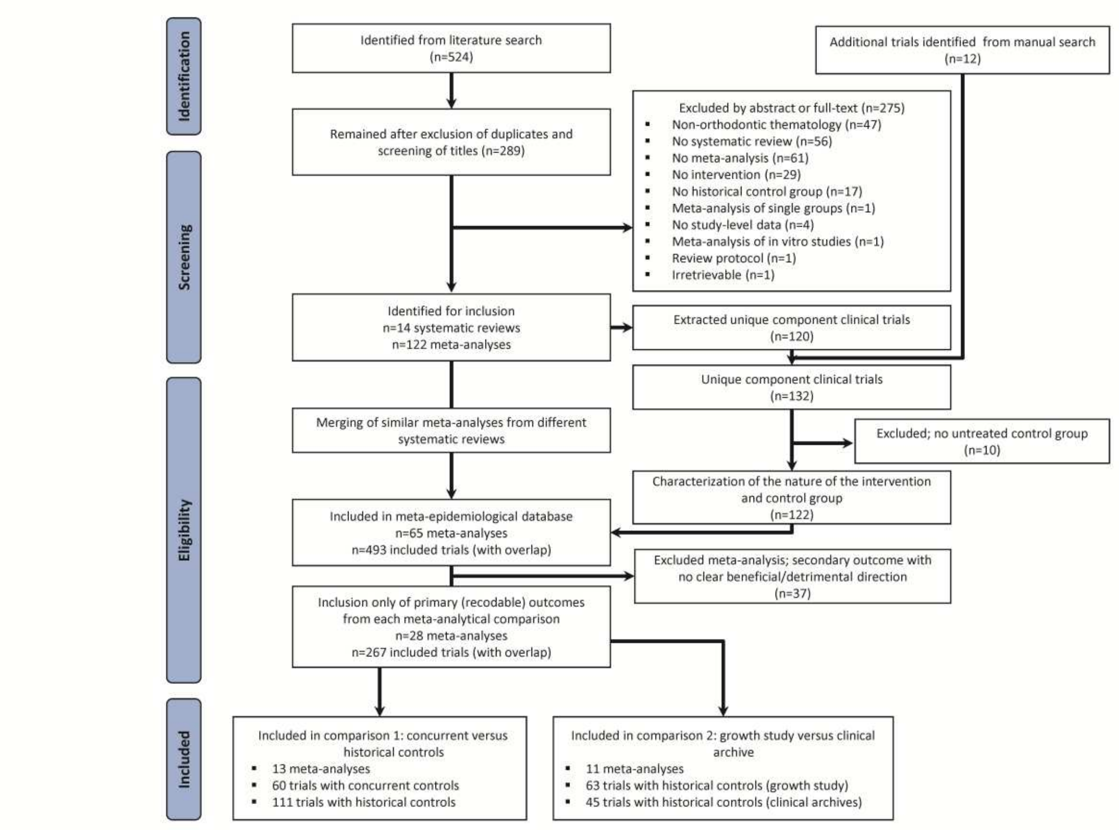

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Figure 2. Forest plot for the meta-epidemiological comparison of studies with concurrent controls and studies with historical controls. MA, meta-analysis; ΔSMD, difference in standardized mean differences; CI, confidence interval.

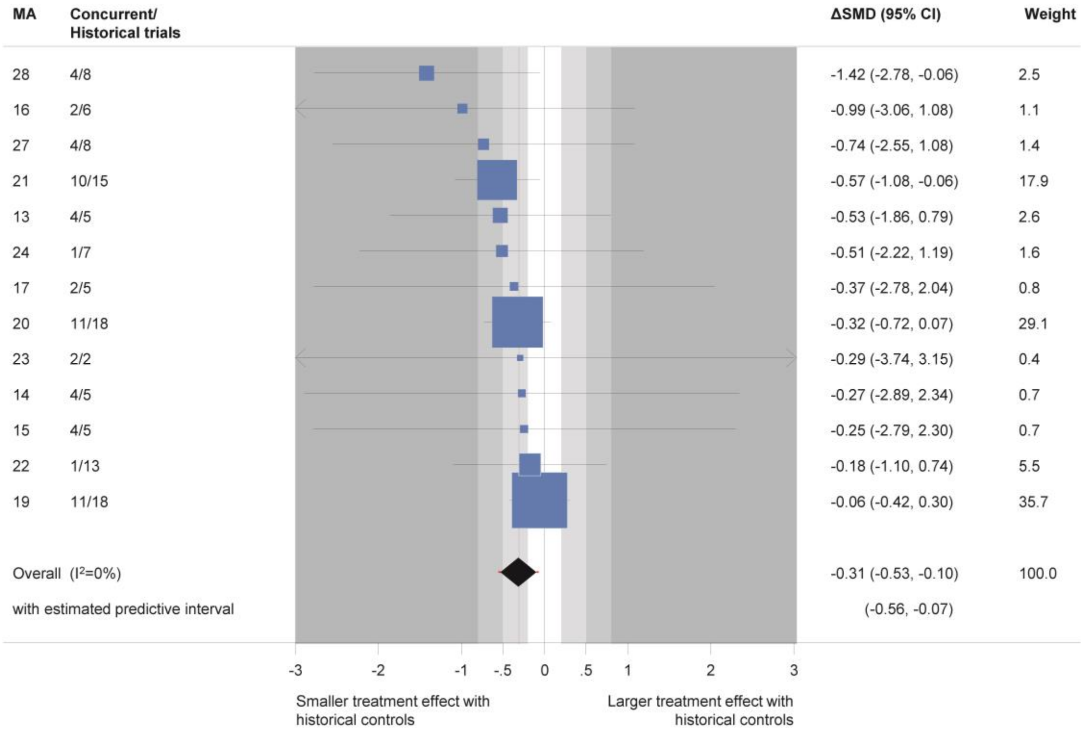

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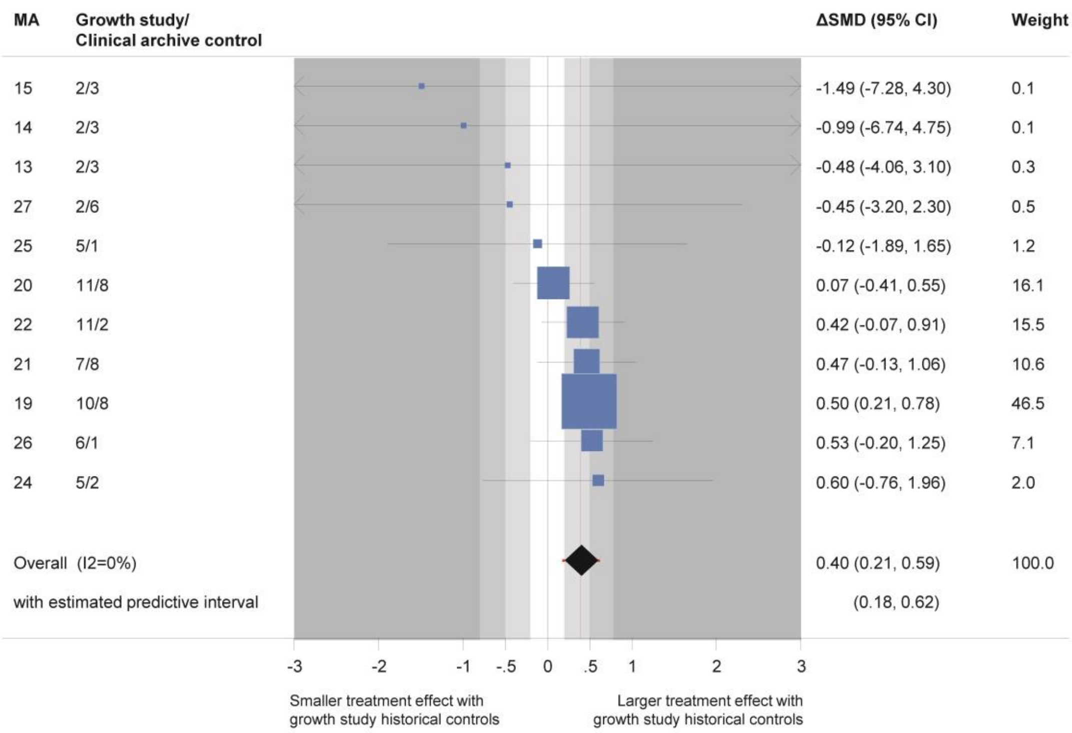
Figure 3. Forest plot for the meta-epidemiological comparison of studies with historical controls from growth studies and studies with historical controls from clinical patient archives. MA, meta-analysis; ΔSMD, difference in standardized mean differences; CI, confidence interval.



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Tables

Table 1. Characteristics of the 122 component trials included in the identified systematic reviews.

Component trials		
Total - n (%)		122 (100%)
Trial design - n (%)		
	Randomized clinical trial	31 (25%)
	Prospective controlled trial	40 (33%)
	Retrospective controlled trial	48 (39%)
	Unclear	3 (3%)
Interventional group		
	Prospective	71 (58%)
	Retrospective	48 (39%)
	Unclear	3 (3%)
Untreated control group		
	Concurrent	45 (37%)
	Historical (growth study)	34 (28%)
	Historical (clinic archive-same source as interventional)	34 (28%)
	Historical (clinic archive-other source as interventional)	7 (6%)
	Unclear	2 (2%)

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Table 2. Results for the meta-epidemiological analyses of the effect of control group on the results of the trial results (expressed as intervention minus control with the standardized mean difference).

Comparison (Cat1 vs Cat2)	MAs	Trials	Trials (Cat1/Cat2)	Effect on trial results			Heterogeneity	
				ΔSMD (95% CI)	P-value	95% predictive interval	I^2 (95% interval)	τ^2
Historical control group (growth study or clinical archive) vs concurrent control group	13	171	111/60	-0.31 (-0.53, -0.10)	**	-0.56, -0.07	0% (0%, 49%)	0
Historical control (growth study) vs historical control (clinic archive)	11	108	63/45	0.40 (0.21, 0.59)	***	0.18, 0.61	0% (0%, 51%)	0

Cat, category; MA, meta-analysis; ΔSMD, difference in standardized mean differences (due to recoding, negative values indicate smaller treatment effect for studies in the first category); CI, confidence interval.
*P<0.05
** P<0.01
***P<0.001

Table 3. Results of the subgroup and sensitivity analyses.

	Historical vs concurrent control			Growth study vs clinical archive historical control		
	MAs	**ΔSMD (95% CI)**	**P_{SG}**	**MAs**	**ΔSMD (95% CI)**	**P_{SG}**
Subgroup analysis						
Class II	8	-0.30 (-0.52, -0.08)	-	8	0.40 (0.21, 0.60)	-
Class III	3	-0.44 (-1.51, 0.64)		3	-0.81 (-3.50, 1.88)	
Transverse deficiency	2	-0.73 (-2.30, 0.85)		-	-	
Sensitivity analysis						
Original (random-effects model)	13	-0.31 (-0.53, -0.10)		11	0.40 (0.21, 0.59)	
Fixed-effect model	13	Same as original		11	Same as original	
One MA per review	4	-0.38 (-0.75, -0.01)		3	0.05 (-0.42, 0.52)	
Most precise MA	1	-0.06 (-0.42, 0.30)		1	0.50 (0.21, 0.78)	
Top 50% precise MAs	6	-0.31 (-0.56, -0.07)		6	0.41 (0.22, 0.61)	

MA, meta-analysis; ΔSMD, difference in standardized mean differences; CI, confidence interval; P_{SG}, P value among subgroups.
*P<0.05
** P<0.01
***P<0.001

Bias from historical control groups used in orthodontic research: a meta-epidemiological study

Supplemental data

Supplementary Table 1. The electronic databases searched, the search strategy used, and the corresponding results (as of July 20th, 2015)

Database	Search Strategy	Filter	Hits
MEDLINE searched through PubMed on March 25th, 2016 http://www.ncbi.nlm.nih.gov/pubmed/	orthodon* AND (control OR untreated)	Systematic Reviews / Meta-analysis	226
Scopus searched on July 20th, 2015 http://www.scopus.com/	orthodon* AND (control OR untreated) AND ("systematic review" OR "meta-analysis")		118
Cochrane Library searched on July 20th, 2015 http://onlinelibrary.wiley.com/cochranelibrary/search	orthodon* AND (control OR untreated)	CDSR & Other Reviews	59
Google Scholar searched on July 20th, 2015 http://www.scholar.google.com/	"orthodontic","meta-analysis","historical control"		52
	"orthodontic","meta-analysis","historic control"		6
	orthodontic,"systematic review","historical control"		53
	orthodontic,"systematic review","historic control"		9
Sum			523

CDSR, Cochrane Database of Systematic Reviews

Supplementary Table 2. List of included and excluded studies, with the corresponding reasons.

EXCLUSION BY ABSTRACT		
Nr.	**Paper**	**Decision with reason**
1	Bergstrand F, Twetman S. Evidence for the efficacy of various methods of treating white-spot lesions after debonding of fixed orthodontic appliances. Journal of clinical orthodontics : JCO. 2003;37(1):19-21.	Excluded; no systematic review
2	Blanck-Lubarsch M, Hohoff A, Wiechmann D, Stamm T. Orthodontic treatment of children/adolescents with special health care needs: an analysis of treatment length and clinical outcome. BMC oral health. 2014;14:67.	Excluded; no systematic review
3	Ng'ang'a PM, Ogaard B. Dental caries and fluorides in relation to fixed orthodontic treatment: a review. East African medical journal. 1993;70(2):75-7.	Excluded; no systematic review
4	Ngiam J, Balasubramaniam R, Darendeliler MA, Cheng AT, Waters K, Sullivan CE. Clinical guidelines for oral appliance therapy in the treatment of snoring and obstructive sleep apnoea. Australian dental journal. 2013;58(4):408-19.	Excluded; no systematic review
5	Chang HP, Tseng YC. Miniscrew implant applications in contemporary orthodontics. Kaohsiung Journal of Medical Sciences. 2014;30(3):111-5.	Excluded; no systematic review
6	Martinez-Mier EA. Fluoride-containing orthodontic adhesives may reduce the occurrence of enamel demineralization in patients with fixed orthodontic appliances. Journal of Evidence-Based Dental Practice. 2011;11(3):132-4.	Excluded; no systematic review
7	Pavoni C, Cozza P. Rational choice of functional/orthopaedic appliances for the correction of class II malocclusion. Mondo Ortodontico. 2011;36(4):146-58.	Excluded; no systematic review
8	AAPD. Guideline on management of the developing dentition and occlusion in pediatric dentistry. Pediatric dentistry. 2005;27(7 Suppl):143-55.	Excluded; no systematic review
9	Abdallah MN, Flores-Mir C. Are interventions for accelerating orthodontic tooth movement effective? Evidence-based dentistry. 2014;15(4):116-7.	Excluded; no systematic review
10	Agence française de sécurité sanitaire des produits de santé AFSSAPS. Prescription of antibiotics for oral and dental care. Medecine et maladies infectieuses. 2012;42(5):193-202.	Excluded; no systematic review
11	Armijo-Olivo S, Cummings GG, Fuentes J, Saltaji H, Ha C, Chisholm A, et al. Identifying items to assess methodological quality in physical therapy trials: a factor analysis. Physical therapy. 2014;94(9):1272-84. Epub 2014/05/03.	Excluded; no systematic review
12	Bretz WA. Oral profiles of bulimic women: Diagnosis and management. What is the evidence? The journal of evidence-based dental practice. 2002;2(4):267-72. Epub 2002/12/01.	Excluded; no systematic review
13	De Pauw GA, Dermaut LR. [Orthodontics based on a new scientific method of evaluating results: "evidence-based"]. L' Orthodontie francaise. 2006;77(2):315-24.	Excluded; no systematic review
14	Flores-Mir C. Does orthodontic treatment lead to gingival recession? Evidence-based dentistry. 2011;12(1):20.	Excluded; no systematic review
15	Flores-Mir C. Grinding is effective in early orthodontic treatment of unilateral posterior crossbite. Evidence-based dentistry. 2005;6(1):24.	Excluded; no systematic review
16	Flores-Mir C. Limited evidence on treatments for distalising upper first molars in children and adolescents. Evidence-based dentistry. 2014;15(1):23-4.	Excluded; no systematic review
17	Gioka C, Eliades T. Materials-induced variation in the torque expression of preadjusted appliances. Am J Orthod Dentofac Orthop. 2004;125(3):323-8.	Excluded; no systematic review
18	Hans MG, Teng CM, Liao CC, Chen YH, Yang CY. An evidence-based approach to treatment of open bite and deep bite: case reports. World journal of orthodontics. 2007;8(1):45-64.	Excluded; no systematic review
19	Hausen H. Oral health promotion reduces plaque and gingival bleeding in the short term. Evidence-based dentistry. 2005;6(2):31.	Excluded; no systematic review
20	Husain J, Burden D, McSherry P, Morris D, Allen M. National clinical guidelines for management of the palatally ectopic maxillary canine. British dental journal. 2012;213(4):171-6.	Excluded; no systematic review
21	Jerrold L, Naghavi N. Evidence-based considerations for determining appointment intervals. Journal of clinical orthodontics : JCO. 2011;45(7):379-83.	Excluded; no systematic review
22	Kalha AS. Medication and tooth movement. Evidence-based dentistry. 2009;10(2):50-1.	Excluded; no systematic review
23	Krieger E, Jacobs C, Walter C, Wehrbein H. Current state of orthodontic patients under bisphosphonate therapy. Head & face medicine. 2013;9:10.	Excluded; no systematic review
24	Laing E, Ashley P, Naini FB, Gill DS. Space maintenance. International journal of paediatric dentistry / the British Paedodontic Society [and] the International Association of Dentistry for Children. 2009;19(3):155-62.	Excluded; no systematic review
25	Liang W, Rong Q, Lin J, Xu B. Torque control of the maxillary incisors in lingual and labial orthodontics: a 3-dimensional finite element analysis. Am J Orthod Dentofac Orthop. 2009;135(3):316-22.	Excluded; no systematic review
26	Lombardo L. Ectopic canine control with conventional brackets. International orthodontics / College europeen d'orthodontie. 2012;10(4):377-403.	Excluded; no systematic review
27	Long H, Jian F, Lai W. Weak evidence supports the short-term benefits of orthopaedic treatment for Class III malocclusion in children. Evidence-based dentistry. 2014;15(1):21-2.	Excluded; no systematic review
28	Long H, Lai W. No reliable evidence for the association between dental crowding and caries. Evidence-based dentistry. 2013;14(1):12.	Excluded; no systematic review
29	Marsicano JA, de Moura-Grec PG, Bonato RC, Sales-Peres Mde C, Sales-Peres A, Sales-Peres SH. Gastroesophageal reflux, dental erosion, and halitosis in epidemiological surveys: a systematic review. European journal of gastroenterology & hepatology. 2013;25(2):135-41.	Excluded; no systematic review
30	O'Neill J. Do lip bumpers work? Evidence-based dentistry. 2009;10(2):48-9.	Excluded; no systematic review

31	O'Neill J. Limited evidence for interceptive extraction of deciduous canines to prevent permanent canine impaction. Evidence-based dentistry. 2011;12(4):106-7. Epub 2011/12/24.	Excluded; no systematic review
32	O'Neill J. Long-term stability after orthodontic treatment remains inconclusive. Evidence-based dentistry. 2007;8(3):81-2. Epub 2007/09/25.	Excluded; no systematic review
33	Pandis N, Polychronopoulou A, Eliades T. An assessment of quality characteristics of randomised control trials published in dental journals. Journal of dentistry. 2010;38(9):713-21. Epub 2010/06/16.	Excluded; no systematic review
34	Paranhos LR, de Magalhaes MP, Francio J, Terada HH, Rosario HD, da Silva RF. Time of guard of orthodontic records versus legal time for their prescription. Dental press journal of orthodontics. 2013;18(3):113-7. Epub 2013/10/08.	Excluded; no systematic review
35	Peltz ID. Evidence lacking to determine whether preoperative analgesic use reduces post dental treatment pain for children. Evidence-based dentistry. 2012;13(4):104. Epub 2012/12/22.	Excluded; no systematic review
36	Proffit WR, Frazier-Bowers SA. Mechanism and control of tooth eruption: overview and clinical implications. Orthodontics & craniofacial research. 2009;12(2):59-66. Epub 2009/05/08.	Excluded; no systematic review
37	Ren Y. Early treatment of skeletal open-bite malocclusion. Evidence-based dentistry. 2006;7(4):103. Epub 2006/12/26.	Excluded; no systematic review
38	Ren Y. Soft tissue changes inconclusive in Class II division 1 patients treated with Activator and Bionator appliances. Evidence-based dentistry. 2007;8(2):49. Epub 2007/06/26.	Excluded; no systematic review
39	Shadrick V, Walker M. Facemask therapy between ages six to ten years may lead to short term improvements for Class III malocclusions. Evidence-based dentistry. 2013;14(4):112-3. Epub 2013/12/21.	Excluded; no systematic review
40	Shah J, Chadwick S. [Comparison of 1-stage orthodontic bonding systems and 2-stage bonding systems: a review of the literature and the results of a randomized clinical trial]. L' Orthodontie francaise. 2009;80(2):167-78.	Excluded; no systematic review
41	Sharif MO, Janjua-Sharif FN, Ali H, Ahmed F. Systematic reviews explained: AMSTAR-how to tell the good from the bad and the ugly. Oral health and dental management. 2013;12(1):9-16. Epub 2013/03/12.	Excluded; no systematic review
42	Williams P, Roberts-Harry D, Sandy J. Orthodontics. Part 7: Fact and fantasy in orthodontics. British dental journal. 2004;196(3):143-8. Epub 2004/02/14.	Excluded; no systematic review
43	Zaoui F. [Light forces and orthodontic displacement: a critical review]. International orthodontics / College europeen d'orthodontie. 2009;7(1):3-13. Epub 2010/03/23. La force legere et le deplacement orthodontique : revue critique.	Excluded; no systematic review
44	Al-Belasy FA, Tozoglu S, Dolwick MF. Mandibular hypomobility after orthognathic surgery: A review article. Journal of Oral and Maxillofacial Surgery. 2013;71(11):1967.e1-.e11.	Excluded; no systematic review
45	Dersot JM. Plaque control, a key element of successful orthodontics. L' Orthodontie francaise. 2010;81(1):33-9.	Excluded; no systematic review
46	Frasson JMD, Magnani MBBDA, Nouer DF, De Siqueira VCV, Lunardi N. Comparative cephalometric study between nasal and predominantly mouth breathers. Revista Brasileira de Otorrinolaringologia. 2006;72(1):72-82.	Excluded; no systematic review
47	Grigore RA, Mihai AM, Ciolan DF, Ţărmure V, Ionescu E. Pain therapy associated with orthodontic treatment. Farmacia. 2014;62(6):1062-71.	Excluded; no systematic review
48	Kuijpers-Jagtman AM. Evidence-based orthodontics, still a long way to go. Nederlands tijdschrift voor tandheelkunde. 2003;110(1):20-4.	Excluded; no systematic review
49	Millett D. Bias in systematic reviews? Journal of orthodontics. 2011;38(3):158-60.	Excluded; no systematic review
50	Monti B, Salvadori S, Tripodi S, Sesso G, Maspero C. Orthodontic anchorage. A literature review. Mondo Ortodontico. 2012;37(5 SUPPL.1):S1-S6.	Excluded; no systematic review
51	Papadopoulos MA. Meta-analysis in evidencebased orthodontics. Orthodontics and Craniofacial Research. 2003;6(2):112-26.	Excluded; no systematic review
52	Ruiz M. Evidence-based orthodontics or the paradigm shift. International Orthodontics. 2011;9(1):1-19.	Excluded; no systematic review
53	Tsukiyama Y, Baba K, Clark GT. An evidence-based assessment of occlusal adjustment as a treatment for temporomandibular disorders. Journal of Prosthetic Dentistry. 2001;86(1):57-66.	Excluded; no systematic review
54	Zhang XG, Yang F, Wu TX, Shi ZD, Yi XZ. Evidence of cochrane systematic reviews on the treatment of temporomandibular disorders. Chinese Journal of Evidence-Based Medicine. 2008;8(12):1130-2.	Excluded; no systematic review
55	Kalemaj Z, Debernard IC, Buti J. Efficacy of surgical and non-surgical interventions on accelerating orthodontic tooth movement: a systematic review. European journal of oral implantology. 2015;8(1):9-24. Epub 2015/03/05.	Excluded; no meta-analysis
56	Abrahamsson C. Masticatory function and temporomandibular disorders in patients with dentofacial deformities. Swedish dental journal Supplement. 2013(231):9-85. Epub 2014/01/15.	Excluded; no meta-analysis
57	Ahrens A, McGrath C, Hagg U. A systematic review of the efficacy of oral appliance design in the management of obstructive sleep apnoea. European journal of orthodontics. 2011;33(3):318-24. Epub 2011/01/18.	Excluded; no meta-analysis
58	Aljabaa A, McDonald F, Newton JT. A systematic review of randomized controlled trials of interventions to improve adherence among orthodontic patients aged 12 to 18. The Angle orthodontist. 2015;85(2):305-13. Epub 2014/07/22.	Excluded; no meta-analysis
59	Andrade DC, Loureiro CA, Araujo VE, Riera R, Atallah AN. Treatment for agenesis of maxillary lateral incisors: a systematic review. Orthodontics & craniofacial research. 2013;16(3):129-36. Epub 2013/02/15.	Excluded; no meta-analysis
60	Aziz T, Flores-Mir C. A systematic review of the association between appliance-induced labial movement of mandibular incisors and gingival recession. Australian orthodontic journal. 2011;27(1):33-9.	Excluded; no meta-analysis
61	Borrie F, Bearn D. Early correction of anterior crossbites: a systematic review. Journal of orthodontics. 2011;38(3):175-84. Epub 2011/08/31.	Excluded; no meta-analysis
62	Camacho AD, Velasquez Cujar SA. Dental movement acceleration: Literature review by an alternative scientific evidence method. World journal of methodology. 2014;4(3):151-62. Epub 2014/10/22.	Excluded; no meta-analysis
63	Chadwick BL, Roy J, Knox J, Treasure ET. The effect of topical fluorides on decalcification in patients with fixed orthodontic appliances: a systematic review. Am J Orthod Dentofac Orthop. 2005;128(5):601-6; quiz	Excluded; no meta-analysis

	70. Epub 2005/11/16.	
64	Farronato G, Kairyte L, Giannini L, Galbiati G, Maspero C. How various surgical protocols of the unilateral cleft lip and palate influence the facial growth and possible orthodontic problems? Which is the best timing of lip, palate and alveolus repair? literature review. Stomatologija / issued by public institution "Odontologijos studija" [et al]. 2014;16(2):53-60. Epub 2014/09/12.	Excluded; no meta-analysis
65	Ferguson KA, Cartwright R, Rogers R, Schmidt-Nowara W. Oral appliances for snoring and obstructive sleep apnea: a review. Sleep. 2006;29(2):244-62. Epub 2006/02/24.	Excluded; no meta-analysis
66	Forst D, Nijjar S, Khaled Y, Lagravere M, Flores-Mir C. Radiographic assessment of external root resorption associated with jackscrew-based maxillary expansion therapies: a systematic review. European journal of orthodontics. 2014;36(5):576-85. Epub 2013/12/21.	Excluded; no meta-analysis
67	Hoogeveen EJ, Jansma J, Ren Y. Surgically facilitated orthodontic treatment: a systematic review. Am J Orthod Dentofac Orthop. 2014;145(4 Suppl):S51-64. Epub 2014/04/01.	Excluded; no meta-analysis
68	Iannetti G, Cascone P, Saltarel A, Ettaro G. Le Fort I in cleft patients: 20 years' experience. The Journal of craniofacial surgery. 2004;15(4):662-9. Epub 2004/06/24.	Excluded; no meta-analysis
69	Iglesias-Linares A, Yanez-Vico RM, Solano-Reina E, Torres-Lagares D, Gonzalez Moles MA. Influence of bisphosphonates in orthodontic therapy: Systematic review. Journal of dentistry. 2010;38(8):603-11. Epub 2010/06/16.	Excluded; no meta-analysis
70	Jacob HB, Buschang PH, dos Santos-Pinto A. Class II malocclusion treatment using high-pull headgear with a splint: a systematic review. Dental press journal of orthodontics. 2013;18(2):21 e1-7. Epub 2013/08/07.	Excluded; no meta-analysis
71	Lopes Filho H, Maia LH, Lau TC, de Souza MM, Maia LC. Early vs late orthodontic treatment of tooth crowding by first premolar extraction: A systematic review. The Angle orthodontist. 2015;85(3):510-7.	Excluded; no meta-analysis
72	Mills JR. The effect of functional appliances on the skeletal pattern. British journal of orthodontics. 1991;18(4):267-75. Epub 1991/11/01.	Excluded; no meta-analysis
73	Nazarali N, Altalibi M, Nazarali S, Major MP, Flores-Mir C, Major PW. Mandibular advancement appliances for the treatment of paediatric obstructive sleep apnea: a systematic review. European journal of orthodontics. 2015. Epub 2015/02/15.	Excluded; no meta-analysis
74	Pazzini CA, Marques LS, Pereira LJ, Correa-Faria P, Paiva SM. Allergic reactions and nickel-free braces: a systematic review. Brazilian oral research. 2011;25(1):85-90. Epub 2011/03/02.	Excluded; no meta-analysis
75	Perinetti G, Primozic J, Castaldo A, Di Lenarda R, Contardo L. Is gingival crevicular fluid volume sensitive to orthodontic tooth movement? A systematic review of split-mouth longitudinal studies. Orthodontics & craniofacial research. 2013;16(1):1-19. Epub 2013/01/15.	Excluded; no meta-analysis
76	Petren S. Correction of unilateral posterior crossbite in the mixed dentition. Studies of treatment effects, stability and cost-effectiveness. Swedish dental journal Supplement. 2011(212):11-83. Epub 2011/09/17.	Excluded; no meta-analysis
77	Pizzo G, Licata ME, Guiglia R, Giuliana G. Root resorption and orthodontic treatment. Review of the literature. Minerva stomatologica. 2007;56(1-2):31-44. Epub 2007/02/09.	Excluded; no meta-analysis
78	Primozic J, Perinetti G, Contardo L, Ovsenik M. Diagnostic performance of 3-dimensional evaluation of palatal vault changes in assessing successful treatment of constricted maxilla in growing subjects. Am J Orthod Dentofac Orthop. 2013;143(1):42-9. Epub 2013/01/01.	Excluded; no meta-analysis
79	Roscoe MG, Meira JB, Cattaneo PM. Association of orthodontic force system and root resorption: A systematic review. Am J Orthod Dentofac Orthop. 2015;147(5):610-26. Epub 2015/04/29.	Excluded; no meta-analysis
80	Rossini G, Parrini S, Castroflorio T, Deregibus A, Debernardi CL. Efficacy of clear aligners in controlling orthodontic tooth movement: A systematic review. The Angle orthodontist. 2014. Epub 2014/11/21.	Excluded; no meta-analysis
81	Viglianisi A. Effects of lingual arch used as space maintainer on mandibular arch dimension: a systematic review. Am J Orthod Dentofac Orthop. 2010;138(4):382 e1-4; discussion -3. Epub 2010/10/05.	Excluded; no meta-analysis
82	Yepes E, Quintero P, Rueda ZV, Pedroza A. Optimal force for maxillary protraction facemask therapy in the early treatment of class III malocclusion. European journal of orthodontics. 2014;36(5):586-94. Epub 2013/12/20.	Excluded; no meta-analysis
83	Bueno Medeiros R, Cardoso de Araújo LF, Mucha JN, Trindade Motta A. Stability of open-bite treatment in adult patients: A systematic review. Journal of the World Federation of Orthodontists. 2012;1(3):e97-e101.	Excluded; no meta-analysis
84	De Rossi M, Rocha RASdS, Gavião MBD. Effects of bonded rapid maxillary expansion appliance (BRMEA) in vertical and sagittal dimensions: A systematic review. Brazilian Journal of Oral Sciences. 2008;7(25):1571-4.	Excluded; no meta-analysis
85	De Toffol L, Pavoni C, Baccetti T, Franchi L, Cozza P. Orthopedic treatment outcomes in Class III malocclusion. Angle Orthodontist. 2008;78(3):561-73.	Excluded; no meta-analysis
86	Hunt OT, Johnston CD, Hepper PG, Burden DJ. The psychosocial impact of orthognathic surgery: A systematic review. American Journal of Orthodontics and Dentofacial Orthopedics. 2001;120(5):490-6.	Excluded; no meta-analysis
87	Marshall SD, Shroff B. Long-term Skeletal Changes with Rapid Maxillary Expansion: A Review of the Literature. Seminars in Orthodontics. 2012;18(2):128-33.	Excluded; no meta-analysis
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89	Walker SL, Tieu LD, Flores-Mir C. Radiographic comparison of the extent of orthodontically induced external apical root resorption in vital and root-filled teeth: A systematic review. European journal of orthodontics. 2013;35(6):796-802.	Excluded; no meta-analysis
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192	Kapoor P, Kharbanda OP, Monga N, Miglani R, Kapila S. Effect of orthodontic forces on cytokine and receptor levels in gingival crevicular fluid: A systematic review. Progress in orthodontics. 2014;15(1):2-21.	Excluded; outcome not eligible for untreated control group
193	Kolokitha OE, Kaklamanos EG, Papadopoulos MA. Prevalence of nickel hypersensitivity in orthodontic patients: A meta-analysis. American Journal of Orthodontics and Dentofacial Orthopedics. 2008;134(6):722.e1-.e12.	Excluded; outcome not eligible for untreated control group
194	Popowich K, Nebbe B, Major PW. Effect of Herbst treatment on temporomandibular joint morphology: A systematic literature review. American Journal of Orthodontics and Dentofacial Orthopedics. 2003;123(4):388-94.	Excluded; outcome not eligible for untreated control group
195	Ahangari Z, Nasser M, Mahdian M, Fedorowicz Z, Marchesan Melissa A. Interventions for the management of external root resorption. Cochrane Database of Systematic Reviews [Internet]. 2010; (6).	Excluded; outcome not eligible for untreated control group
196	Al Ani Z, Gray RJ, Davies SJ, Sloan P, Glenny AM. Stabilization splint therapy for the treatment of temporomandibular myofascial pain: a systematic review (Structured abstract). Journal of dental education [Internet]. 2005; (11):[1242-50 pp.].	Excluded; outcome not eligible for untreated control group
197	Angelopoulou MV, Vlachou V, Halazonetis DJ. Pharmacological management of pain during orthodontic treatment: a meta-analysis (Provisional abstract). Orthodontics and Craniofacial Research [Internet]. 2012; (2):[71-83 pp.].	Excluded; outcome not eligible for untreated control group
198	Belmonte Flavia M, Macedo Cristiane R, Day Peter F, Saconato H, Fernandes Moça Trevisani V. Interventions for treating traumatised permanent front teeth: luxated (dislodged) teeth. Cochrane Database of Systematic Reviews [Internet]. 2013; (4).	Excluded; outcome not eligible for untreated control group
199	Bollen AM, Cunha-Cruz J, Bakko DW, Huang GJ, Hujoel PP. The effects of orthodontic therapy on periodontal health: a systematic review of controlled evidence (Structured abstract). Journal of the American Dental Association [Internet]. 2008; (4):[413-22 pp.].	Excluded; outcome not eligible for untreated control group

200	Carvalho Fernando R, Lentini-Oliveira Débora A, Machado Marco Antonio C, Saconato H, Prado Lucila BF, Prado Gilmar F. Oral appliances and functional orthopaedic appliances for obstructive sleep apnoea in children. Cochrane Database of Systematic Reviews [Internet]. 2007; (2).	Excluded; outcome not eligible for untreated control group
201	Fedorowicz Z, Nasser M, Newton T, Oliver R. Resorbable versus titanium plates for orthognathic surgery. Cochrane Database of Systematic Reviews [Internet]. 2007; (2).	Excluded; outcome not eligible for untreated control group
202	Fleming PS, Fedorowicz Z, Johal A, El-Angbawi A, Pandis N. Surgical adjunctive procedures for accelerating orthodontic treatment. Cochrane Database of Systematic Reviews [Internet]. 2015; (6).	Excluded; outcome not eligible for untreated control group
203	Fleming PS, Eliades T, Katsaros C, Pandis N. Curing lights for orthodontic bonding: a systematic review and meta-analysis (Provisional abstract). American Journal of Orthodontics and Dentofacial Orthopedics [Internet]. 2013; (4):[S92-s103 pp.].	Excluded; outcome not eligible for untreated control group
204	Fleming PS, Johal A, Pandis N. Self-etch primers and conventional acid-etch technique for orthodontic bonding: a systematic review and meta-analysis (Provisional abstract). American Journal of Orthodontics and Dentofacial Orthopedics [Internet]. 2012; (1):[83-94 pp.].	Excluded; outcome not eligible for untreated control group
205	Hu H, Li C, Li F, Chen J, Sun J, Zou S, et al. Enamel etching for bonding fixed orthodontic braces. Cochrane Database of Systematic Reviews [Internet]. 2013; (11).	Excluded; outcome not eligible for untreated control group
206	Jian F, Lai W, Furness S, McIntyre Grant T, Millett Declan T, Hickman J, et al. Initial arch wires for tooth alignment during orthodontic treatment with fixed appliances. Cochrane Database of Systematic Reviews [Internet]. 2013; (4).	Excluded; outcome not eligible for untreated control group
207	Li X, Tang Y, Chen Y. Interventions for pain during fixed orthodontic appliance therapy: a systematic review (Provisional abstract). Angle Orthodontist [Internet]. 2010; (5):[925-32 pp.].	Excluded; outcome not eligible for untreated control group
208	Long H, Pyakurel U, Wang Y, Liao L, Zhou Y, Lai W. Interventions for accelerating orthodontic tooth movement: a systematic review (Provisional abstract). Angle Orthodontist [Internet]. 2013; (1):[164-71 pp.].	Excluded; outcome not eligible for untreated control group
209	Mandall Nicky A, Hickman J, Macfarlane Tatiana V, Mattick Rye CR, Millett Declan T, Worthington Helen V. Adhesives for fixed orthodontic brackets. Cochrane Database of Systematic Reviews [Internet]. 2003; (2).	Excluded; outcome not eligible for untreated control group
210	Millett Declan T, Mandall Nicky A, Mattick Rye CR, Hickman J, Glenny A-M. Adhesives for bonded molar tubes during fixed brace treatment. Cochrane Database of Systematic Reviews [Internet]. 2011; (6).	Excluded; outcome not eligible for untreated control group
211	Parkin N, Benson Philip E, Thind B, Shah A. Open versus closed surgical exposure of canine teeth that are displaced in the roof of the mouth. Cochrane Database of Systematic Reviews [Internet]. 2008; (4).	Excluded; outcome not eligible for untreated control group
212	Riley M, Bearn DR. A systematic review of clinical trials of aligning archwires (Structured abstract). Journal of orthodontics [Internet]. 2009; (1):[42-51 pp.].	Excluded; outcome not eligible for untreated control group

EXCLUSION BY FULLTEXT

Nr.	Paper	Decision with reason
1	Toffol LD, Pavoni C, Baccetti T, Franchi L, Cozza P. Orthopedic treatment outcomes in Class III malocclusion. A systematic review. Angle Orthod 2008;78(3):561-73.	Excluded; no systematic review
2	Barnett GA, Higgins DW, Major PW, Flores-Mir C. Immediate skeletal and dentoalveolar effects of the crown- or banded type herbst appliance on class II division 1 malocclusion. Angle Orthodontist. 2008;78(2):361-9.	Excluded; no meta-analysis
3	Cozza P, Baccetti T, Franchi L, De Toffol L, McNamara JA, Jr. Mandibular changes produced by functional appliances in Class II malocclusion: a systematic review. Am J Orthod Dentofac Orthop 2006;129(5):599 e1-12.	Excluded; no meta-analysis
4	Cozza P, Mucedero M, Baccetti T, Franchi L. Early orthodontic treatment of skeletal open-bite malocclusion: a systematic review. Angle Orthod 2005;75(5):707-13.	Excluded; no meta-analysis
5	Flores-Mir C, Ayeh A, Goswani A, Charkhandeh S. Skeletal and dental changes in Class II division 1 malocclusions treated with splint-type Herbst appliances. A systematic review. Angle Orthod 2007;77(2):376-81.	Excluded; no meta-analysis
6	Flores-Mir C, Major PW. A systematic review of cephalometric facial soft tissue changes with the Activator and Bionator appliances in Class II division 1 subjects. Eur J Orthod 2006;28(6):586-93.	Excluded; no meta-analysis
7	Flores-Mir C, Major PW. Cephalometric facial soft tissue changes with the twin block appliance in Class II division 1 malocclusion patients. A systematic review. Angle Orthod 2006;76(5):876-81.	Excluded; no meta-analysis
8	Lagravere MO, Major PW, Flores-Mir C. Long-term dental arch changes after rapid maxillary expansion treatment: a systematic review. Angle Orthod 2005;75(2):155-61.	Excluded; no meta-analysis
9	Lagravere MO, Major PW, Flores-Mir C. Long-term skeletal changes with rapid maxillary expansion: a systematic review. Angle Orthod 2005;75(6):1046-52.	Excluded; no meta-analysis
10	Lagravere MO, Major PW, Flores-Mir C. Skeletal and dental changes with fixed slow maxillary expansion treatment: a systematic review. J Am Dent Assoc 1939 2005;136(2):194-9.	Excluded; no meta-analysis
11	Lentini-Oliveira DA, Carvalho FR, Ye Q, Luo J, Saconato H, Machado MAC, et al. Orthodontic and orthopaedic treatment for anterior open bite in children. Cochrane Database Syst Rev 2007(2).	Excluded; no meta-analysis
12	Littlewood SJ, Millett DT, Doubleday B, Bearn DR, Worthington HV. Retention procedures for stabilising tooth position after treatment with orthodontic braces. Cochrane Database Syst Rev 2006(1):CD002283.	Excluded; no meta-analysis

13	Mandall NA, Millett DT, Mattick CR, Hickman J, Worthington HV, Macfarlane TV. Orthodontic adhesives: a systematic review. J Orthod 2002;29(3):205-10.	Excluded; no meta-analysis
14	Millett Declan T, Cunningham S, O'Brien Kevin D, Benson Philip E, Williams A, de Oliveira Cesar M. Orthodontic treatment for deep bite and retroclined upper front teeth in children. Cochrane Database Syst Rev [Internet]. 2006; (4).	Excluded; no meta-analysis
15	Millett DT, Cunningham SJ, O'Brien KD, Benson PE, de Oliveira CM. Treatment and stability of class II division 2 malocclusion in children and adolescents: a systematic review. Am J Orthod Dentofac Orthop 2012;142(2):159-69 e9.	Excluded; no meta-analysis
16	Minami-Sugaya H, Lentini-Oliveira Débora A, Carvalho Fernando R, Machado Marco Antonio C, Marzola C, Saconato H, et al. Treatments for adults with prominent lower front teeth. Cochrane Database Syst Rev 2012; (5).	Excluded; no meta-analysis
17	Mucedero M, Coviello A, Baccetti T, Franchi L, Cozza P. Stability factors after double-jaw surgery in Class III malocclusion. A systematic review. Angle Orthod 2008;78(6):1141-52.	Excluded; no meta-analysis
18	Petren S, Bondemark L, Soderfeldt B. A systematic review concerning early orthodontic treatment of unilateral posterior crossbite. Angle Orthod 2003;73(5):588-96.	Excluded; no meta-analysis
19	Skeggs RM, Benson PE, Dyer F. Reinforcement of anchorage during orthodontic brace treatment with implants or other surgical methods. Cochrane Database Syst Rev 2007(3):CD005098.	Excluded; no meta-analysis
20	Weltman B, Vig KW, Fields HW, Shanker S, Kaizar EE. Root resorption associated with orthodontic tooth movement: a systematic review. Am J Orthod Dentofac Orthop 2010;137(4):462-76.	Excluded; no meta-analysis
21	Yu Y, Sun J, Lai W, Wu T, Koshy S, Shi Z. Interventions for managing relapse of the lower front teeth after orthodontic treatment. Cochrane Database Syst Rev 2013; (9).	Excluded; no meta-analysis
22	Cordasco G, Matarese G, Rustico L, Fastuca S, Caprioglio A, Lindauer SJ, et al. Efficacy of orthopedic treatment with protraction facemask on skeletal Class III malocclusion: A systematic review and meta-analysis. Orthod Craniofac Res 2014;17(3):133-43.	Excluded; no untreated control group
23	Fan L, Kuang Q, Tang Y, Qin P. [Effect of premolar extractions on third molar angulation changes: a meta-analysis]. Zhong nan da xue xue bao Yi xue ban = Journal of Central South University Medical sciences. 2015;40(3):317-25.	Excluded; no untreated control group
24	Flores-Mir C, Major MP, Major PW. Soft tissue changes with fixed functional appliances in Class II division 1. Angle Orthod 2006;76(4):712-20.	Excluded; no untreated control group
25	Harrison JE, Ashby D. Orthodontic treatment for posterior crossbites. Cochrane Database Syst Rev 2001(1):CD000979.	Excluded; no untreated control group
26	Harrison JE, O'Brien KD, Worthington HV. Orthodontic treatment for prominent upper front teeth in children. Cochrane Database Syst Rev 2007(3):CD003452.	Excluded; no untreated control group
27	Jambi S, Thiruvenkatachari B, O'Brien KD, Walsh T. Orthodontic treatment for distalising upper first molars in children and adolescents. Cochrane Database Syst Rev 2013;10:CD008375.	Excluded; no untreated control group
28	Koretsi V, Chatzigianni A, Sidiropoulou S. Enamel roughness and incidence of caries after interproximal enamel reduction: a systematic review. Orthod Craniofac Res 2014;17(1):1-13.	Excluded; no untreated control group
29	Leite RA, Rodrigues JF, Sakima MT, Sakima T. Relationship between temporomandibular disorders and orthodontic treatment: a literature review. Dental Press J Orthod 2013;18(1):150-7.	Excluded; no untreated control group
30	Li F, Hu HK, Chen JW, Liu ZP, Li GF, He SS, et al. Comparison of anchorage capacity between implant and headgear during anterior segment retraction. Angle Orthod 2011; (5):915-22.	Excluded; no untreated control group
31	Marsico E, Gatto E, Burrascano M, Matarese G, Cordasco G. Effectiveness of orthodontic treatment with functional appliances on mandibular growth in the short term. Am J Orthod Dentofac Orthop 2011;139(1):24-36.	Excluded; no untreated control group
32	Papadopoulos MA, Papageorgiou SN, Zogakis IP. Clinical effectiveness of orthodontic miniscrew implants: a meta-analysis. J Dent Res 2011;(8):969-76.	Excluded; no untreated control group
33	Sunnak R, Johal A, Fleming PS. Is orthodontics prior to 11 years of age evidence-based? A systematic review and meta-analysis. J Dent 2015;43(5):477-86.	Excluded; no untreated control group
34	Thiruvenkatachari B, Harrison Jayne E, Worthington Helen V, O'Brien Kevin D. Orthodontic treatment for prominent upper front teeth (Class II malocclusion) in children. Cochrane Database Syst Rev 2013; (11).	Excluded; no untreated control group
35	Watkinson S, Harrison JE, Furness S, Worthington HV. Orthodontic treatment for prominent lower front teeth (Class III malocclusion) in children. Cochrane Database Syst Rev 2013;9:CD003451.	Excluded; no untreated control group
36	Greenlee GM, Huang GJ, Chen SS, Chen J, Koepsell T, Hujoel P. Stability of treatment for anterior open-bite malocclusion: a meta-analysis. Am J Orthod Dentofac Orthop 2011;139(2):154-69.	Excluded; meta-analysis of single group estimates (no comparisons made)
37	Antonarakis GS, Kiliaridis S. Short-term anteroposterior treatment effects of functional appliances and extraoral traction on class II malocclusion. A meta-analysis. Angle Orthod 2007;77(5):907-14.	Excluded; no study-level data available
38	Chen JY, Will LA, Niederman R. Analysis of efficacy of functional appliances on mandibular growth. Am J Orthod Dentofac Orthop 2002;122(5):470-6.	Excluded; no study-level data available
39	Perillo L, Cannavale R, Ferro F, Franchi L, Masucci C, Chiodini P, et al. Meta-analysis of skeletal mandibular changes during Frankel appliance treatment. Eur J Orthod 2011;33(1):84-92.	Excluded; no study-level data available
40	Niu Y, Zhou H. [Effect on functional appliances on mandibular growth on skeletal Class II malocclusion: a systematic review]. Hua xi kou qiang yi xue za zhi = Huaxi kouqiang yixue zazhi = West China journal of stomatology. 2011;29(4):384-8.	Excluded; no study-level data available
41	Al-Jewair TS. Meta-analysis on the mandibular dimensions effects of the MARA appliance in patients with Class II malocclusions. Angle Orthod 2015;85(4):706-14.	Included
42	Chatzoudi MI, Ioannidou-Marathiotou I, Papadopoulos MA. Clinical effectiveness of chin cup treatment for the management of Class III malocclusion in pre-pubertal patients: a systematic review and meta-analysis. Prog Orthod 2014;15:62.	Included

43	Ehsani S, Nebbe B, Normando D, Lagravere MO, Flores-Mir C. Short-term treatment effects produced by the Twin-block appliance: a systematic review and meta-analysis. Eur J Orthod 2015;37(2):170-6.	Included
44	Feng X, Li J, Li Y, Zhao Z, Zhao S, Wang J. Effectiveness of TAD-anchored maxillary protraction in late mixed dentition. Angle Orthod 2012;82(6):1107-14.	Included
45	Foersch M, Jacobs C, Wriedt S, Hechtner M, Wehrbein H. Effectiveness of maxillary protraction using facemask with or without maxillary expansion: a systematic review and meta-analysis. Clin Oral Investig. 2015 Jul;19(6):1181-92.	Included
46	Koretsi V, Zymperdikas VF, Papageorgiou SN, Papadopoulos MA. Treatment effects of removable functional appliances in patients with Class II malocclusion: a systematic review and meta-analysis. Eur J Orthod 2014.	Included
47	Liu ZP, Li CJ, Hu HK, Chen JW, Li F, Zou SJ. Efficacy of short-term chincup therapy for mandibular growth retardation in Class III malocclusion. Angle Orthod 2011;81(1):162-68.	Included
48	Perinetti G, Primožič J, Furlani G, Franchi L, Contardo L. Treatment effects of fixed functional appliances alone or in combination with multibracket appliances: A systematic review and meta-analysis. Angle Orthod. 2015 May;85(3):480-92.	Included
49	Yang X, Li C, Bai D, Su N, Chen T, Xu Y, Han X. Treatment effectiveness of Fränkel function regulator on the Class III malocclusion: a systematic review and meta-analysis. Am J Orthod Dentofacial Orthop 2014;146(2):143-54.	Included
50	Zhang W, Qu HC, Yu M, Zhang Y. The Effects of Maxillary Protraction with or without Rapid Maxillary Expansion and Age Factors in Treating Class III Malocclusion: A Meta-Analysis. PloS one 2015;10(6):e0130096.	Included
51	Zhou Y, Long H, Ye N, Xue J, Yang X, Liao L, et al. The effectiveness of non-surgical maxillary expansion: a meta-analysis. Eur J Orthod 2014;36(2):233-42.	Included
52	Zymperdikas VF, Koretsi V, Papageorgiou SN, Papadopoulos MA. Treatment effects of fixed functional appliances in patients with Class II malocclusion: a systematic review and meta-analysis. Eur J Orthod 2015.	Included

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Nr.	Paper	Decision with reason
1	Araújo MM, Martins CC, Costa LC, Cota LO, Faria RL, Cunha FA, Costa FO. Association between depression and periodontitis: a systematic review and meta-analysis. J Clin Periodontol. 2016 Mar;43(3):216-28.	Excluded; not relevant
2	Avila WM, Pordeus IA, Paiva SM, Martins CC. Breast and Bottle Feeding as Risk Factors for Dental Caries: A Systematic Review and Meta-Analysis. PLoS One. 2015 Nov 18;10(11):e0142922.	Excluded; not relevant
3	Castroflorio T, Bargellini A, Rossini G, Cugliari G, Rainoldi A, Deregibus A. Risk factors related to sleep bruxism in children: A systematic literature review. Arch Oral Biol. 2015 Nov;60(11):1618-24.	Excluded; not relevant
4	Corrêa-Faria P, Petti S. Are overweight/obese children at risk of traumatic dental injuries? A meta-analysis of observational studies. Dent Traumatol. 2015 Aug;31(4):274-82.	Excluded; not relevant
5	Cury JA, de Oliveira BH, Dos Santos AP, Tenuta LM. Are fluoride releasing dental materials clinically effective on caries control? Dent Mater. 2016 Mar;32(3):323-33.	Excluded; not relevant
6	Esteves Lima RP, Cyrino RM, de Carvalho Dutra B, Oliveira da Silveira J, Martins CC, Miranda Cota LO, Costa FO. Association Between Periodontitis and Gestational Diabetes Mellitus: Systematic Review and Meta-Analysis. J Periodontol. 2016 Jan;87(1):48-57.	Excluded; not relevant
7	Guo Y, Zhou S, Liu F, Zhang B. CYP2E1 RsaI/PstI polymorphisms contributed to oral cancer susceptibility: a meta-analysis. Int J Clin Exp Pathol. 2015 Nov 1;8(11):14685-92	Excluded; not relevant
8	Huang C, Somar M, Li K, Mohadeb JV. Efficiency of Cordless Versus Cord Techniques of Gingival Retraction: A Systematic Review. J Prosthodont. [Epub ahead of print].	Excluded; not relevant
9	Schwarz F, Becker K, Renvert S. Efficacy of air polishing for the non-surgical treatment of peri-implant diseases: a systematic review. J Clin Periodontol. 2015 Oct;42(10):951-9.	Excluded; not relevant
10	Yin XH, Wang YD, Luo H, Zhao K, Huang GL, Luo SY, Peng JX, Song JK. Association between Tooth Loss and Gastric Cancer: A Meta-Analysis of Observational Studies. PLoS One. 2016 Mar 2;11(3):e0149653.	Excluded; not relevant
11	Zhu M, Li J, Chen B, Mei L, Yao L, Tian J, Li H. The Effect of Calcium Sodium Phosphosilicate on Dentin Hypersensitivity: A Systematic Review and Meta-Analysis. PLoS One. 2015 Nov 6;10(11):e0140176.	Excluded; not relevant
12	Nazarali N, Altalibi M, Nazarali S, Major MP, Flores-Mir C, Major PW. Mandibular advancement appliances for the treatment of paediatric obstructive sleep apnea: a systematic review. Eur J Orthod. 2015 Dec;37(6):618-26.	Excluded; already identified
13	Ren C, McGrath C, Yang Y. The effectiveness of low-level diode laser therapy on orthodontic pain management: a systematic review and meta-analysis. Lasers Med Sci. 2015 Sep;30(7):1881-93.	Excluded; already identified
14	Rossini G, Parrini S, Castroflorio T, Deregibus A, Debernardi CL. Efficacy of clear aligners in controlling orthodontic tooth movement: a systematic review. Angle Orthod. 2015 Sep;85(5):881-9.	Excluded; already identified
15	Li FJ, Zhang JY, Zeng XT, Guo Y. Low-level laser therapy for orthodontic pain: a systematic review. Lasers Med Sci. 2015 Aug;30(6):1789-803.	Excluded; already identified
16	Koretsi V, Zymperdikas VF, Papageorgiou SN, Papadopoulos MA. Treatment effects of removable functional appliances in patients with Class II malocclusion: a systematic review and meta-analysis. Eur J Orthod. 2015 Aug;37(4):418-34.	Excluded; already identified

17	Meursinge Reynders R, Ronchi L, Ladu L, Di Girolamo N, de Lange J, Roberts N, Mickan S. Barriers and facilitators to the implementation of orthodontic mini-implants in clinical practice: a protocol for a systematic review and meta-analysis. Syst Rev. 2016 Feb 5;5(1):22.	Excluded; review protocol
18	Bazargani F, Magnuson A, Löthgren H, Kowalczyk A. Orthodontic bonding with and without primer: a randomized controlled trial. Eur J Orthod. 2015 [Epub ahead of print].	Excluded; no review
19	Altmann AS, Collares FM, Leitune VC, Samuel SM. The effect of antimicrobial agents on bond strength of orthodontic adhesives: a meta-analysis of in vitro studies. Orthod Craniofac Res. 2016 Feb;19(1):1-9.	Excluded; review of in vitro studies
20	Nascimento PL, Fernandes MT, Figueiredo FE, Faria-E-Silva AL. Fluoride-Releasing Materials to Prevent White Spot Lesions around Orthodontic Brackets: A Systematic Review. Braz Dent J. 2016 Feb;27(1):101-107.	Excluded; not retrievable
21	Alsafadi AS, Alabdullah MM, Saltaji H, Abdo A, Youssef M. Effect of molar intrusion with temporary anchorage devices in patients with anterior open bite: a systematic review. Prog Orthod. 2016 Dec;17(1):9.	Excluded; no meta-analysis
22	Al-Saleh MA, Alsufyani N, Flores-Mir C, Nebbe B, Major PW. Changes in temporomandibular joint morphology in class II patients treated with fixed mandibular repositioning and evaluated through 3D imaging: a systematic review. Orthod Craniofac Res. 2015 Nov;18(4):185-201.	Excluded; no meta-analysis
23	El-Angbawi A, McIntyre GT, Fleming PS, Bearn DR. Non-surgical adjunctive interventions for accelerating tooth movement in patients undergoing fixed orthodontic treatment. Cochrane Database Syst Rev. 2015 Nov 18;11:CD010887.	Excluded; no meta-analysis
24	Iodice G, Danzi G, Cimino R, Paduano S, Michelotti A. Association between posterior crossbite, skeletal, and muscle asymmetry: a systematic review. Eur J Orthod. 2016 [Epub ahead of print].	Excluded; no meta-analysis
25	Yao J, Li DD, Yang YQ, McGrath CP, Mattheos N. What are patients' expectations of orthodontic treatment: a systematic review. BMC Oral Health. 2016 Feb 17;16(1):19. doi: 10.1186/s12903-016-0182-3.	Excluded; no meta-analysis
26	Poorsattar-Bejeh Mir K, Poorsattar-Bejeh Mir A, Poorsattar-Bejeh Mir M, Moradi-Lakeh M, Balmeh P, Nosrati K. Rapid Palatal Expansion to Treat Nocturnal Enuretic Children: a Systematic Review and Meta-Analysis. J Dent (Shiraz). 2015 Sep;16(3):138-48.	Excluded; no untreated control group
27	Zhou Q, Ul Haq AA, Tian L, Chen X, Huang K, Zhou Y. Canine retraction and anchorage loss self-ligating versus conventional brackets: a systematic review and meta-analysis. BMC Oral Health. 2015 Nov 4;15(1):136.	Excluded; no untreated control group
28	Zhu Y, Long H, Jian F, Lin J, Zhu J, Gao M, Lai W. The effectiveness of oral appliances for obstructive sleep apnea syndrome: A meta-analysis. J Dent. 2015 Dec;43(12):1394-402.	Excluded; no untreated control group
29	Feres MF, Raza H, Alhadlaq A, El-Bialy T. Rapid maxillary expansion effects in Class II malocclusion: a systematic review. Angle Orthod. 2015 Nov;85(6):1070-9.	Excluded; only one study with control group
30	Perinetti G, Primožič J, Franchi L, Contardo L. Treatment Effects of Removable Functional Appliances in Pre-Pubertal and Pubertal Class II Patients: A Systematic Review and Meta-Analysis of Controlled Studies. PLoS One. 2015 Oct 28;10(10):e0141198.	Included
31	Papageorgiou SN, Kutschera E, Memmert S, Gölz L, Jäger A, Bourauel C, Eliades T. Effectiveness of early orthopedic treatment with headgear: a systematic review and meta-analysis. Eur J Orthod 2016 (submitted).	Manual addition; included

Supplementary Table 3. Characteristics of the included systematic reviews

Nr	Systematic review	PMID	Problem	Intervention	Included studies	Extracted meta-analyses
1	Al-Jewair	25181253	Class II malocclusion	Functional appliance (MARA appliance)	7	3
2	Chatzoudi et al.	25679781	Class III malocclusion	Chincup	5	13
3	Ehsani et al.	25052373	Class II malocclusion	Functional appliance (Twin Block appliance)	10	6
4	Feng et al.	22458766	Class III malocclusion	Skeletal-anchored maxillary protraction	4	1
5	Foersch et al.	25982454	Class III malocclusion	Maxillary protraction (with/without maxillary expansion or maxillary expansion/constriction)	8	13
6	Koretsi et al.	25398303	Class II malocclusion	Functional appliances (removable appliances)	19	28
7	Liu et al.	20936970	Class III malocclusion	Chincup	4	2
8	Papageorgiou et al.	_R999971	Class II malocclusion	Headgear	15	2
9	Perinetti et al.	25188504	Class II malocclusion	Functional appliances (fixed appliances)	12	5
10	Perinetti et al.*	26510187	Class II malocclusion	Functional appliances (removable appliances)	11	0
11	Yang et al.	25085296	Class III malocclusion	Functional appliances (Fränkel appliance)	6	5
12	Zhang et al.	26068221	Class III malocclusion	Maxillary protraction (with/without maxillary expansion)	12	10
13	Zhou et al.	23828862	Transversal discrepancy	Maxillary expansion	14	7
14	Zymperdikas et al.	25995359	Class II malocclusion	Functional appliances (fixed appliances)	10	27

*No new meta-analysis added; additional studies added from this systematic review in the existing meta-analyses.

Supplementary Table 4. Design of the included trials.

Nr	Trial	PMID	Design		Experimental		Control	
			Code 1-RCT 2-pCCT 3-rCCT	Text	Code 1-Prosp 2-Retro	Text	Code 1-Concurrent 2-Growth study 3-Archive-same 4-Archive-other	Text
1	Abdelnaby and Nassar 2010	20578869	1	The patients were randomly divided into three groups.	1	Same as Design.	1	In group 3, the patients did not receive any orthodontic or orthopedic treatment during the study period.
2	Abu Alhaija and Richardson 1999	10407538	3	The material for the study comprised lateral cephalometric radiographs of 23 patients (14 males, nine females) with a Class III relationship of the incisor teeth treated with the chincap.	2	Same as Design. The records (of the exper. group) consisted of three cephalometric radiographs.	3	Each treated (chincap) patient was matched before treatment with a Class III (control) subject for the Wits measurement of skeletal discrepancy to within 0.1 mm, sex and dental stage. Control subjects received no treatment during the period of the investigation. The control subjects had two records.
3	Akkaya et al 1998	9699403	Exclude	-	-	-	-	No untreated control
4	Alali 2014	23987240	1	All subjects were randomized by the author at the beginning of the study to either the treatment or control \group.	1	Same as Design.	1	Same as Design.
5	Al-Jewair et al 2012	22214390	3	A retrospective study was conducted using lateral cephalograms of patients consecutively treated with MARA (n540) and AdvanSync...	2	Forty (22 males, 18 females) MARA patient records obtained from the cases treated by the developer of the appliance, and 30 (13 males, 17 females) AdvanSync obtained from one author (Dr Dischinger) were included	2	Results were compared with 24 (13 males, 11 females) untreated control individuals obtained from the University of Michigan Growth Study Center and matched with the treatment groups for skeletal age, sex, and craniofacial morphology.
6	Almeida 2004	14994884	3	The purpose of this retrospective	2	Same as Design	3	The control sample was obtained from the files of the Orthodontic Department longitudinal growth study at the Bauru Dental School, University of São Paulo, Brazil….
7	Almeida-Pedrin et al 2007	17693369	2 (?)	This prospective clinical study was designed to evaluate cephalometrically	1 (?)	The experimental sample was collected by random evaluation by 1 operator.	3	The control sample was obtained from the files of the Orthodontic Department at Bauru Dental School, University of Sao Paulo
8	Altug et al 1989	2489495	Unclear	-	-	-	-	-
9	Andreoli 2008	_R999989	1	A amostra inicialmente teve um caráter prospectivo, em que os paciente foram selecionados e tratados por um único profissional, com uma divisão aleatória entre os grupos tratado e controle. Foram utilizados também somente dois aparelhos de raios-x, e devido a isto todas as medições foram compensadas pelo fator de magnificação, sendo que as obtenções radiográficas foram feitas pelo mesmo operador técnico.	1	Same as Design.	1	Same as Design.
10	Angelieri et al 2014	23736378	2	: a prospective evalution 7 years post-treatment	1	The FR-2 sample was collected prospectively and was comprised	2	The cephalograms of the untreated subjects were obtained from the University of Michigan Growth Study and the Denver Child Growth Study
11	Arman 2006	16731542	3	The material consisted of the cephalograms and hand-wrist films of 14 subjects (9 girls, 5 boys) treated in the Department of Orthodontics	2	Same as Design	2 (?)	..and 15 untreated control subjects (10 girls, 5 boys) from a previously collected longitudinal growth study.
12	Arman et al 2004	15673133	3	The records included in the treatment groups were selected retrospectively.	2	Same as Design.	2	and of 20 nontreated control subjects from a previously collected longitudinal growth study. The control subjects mostly presented skeletal Class I relationships for ethical purposes; thus, statistical differences in some of the parameters between control and treatment groups were noted
13	Baccetti 1998	9517727	3	A parent sample of records from 105 patients with Class III malocclusion treated with maxillary expansion (bonded maxillary expander) and face-mask therapy was obtained from North American practitioners experienced in this type of treatment	2	Same as Design	4	Thirty-two subjects (18 female, 14 male) with untreated Class III malocclusion were selected from the files of the Department of Orthodontics of the University of Florence to make up the control group.
14	Baccetti et al 2000;118:159-70	10935956	3	The cephalometric records of 79 patients treated with the Twin-block appliance were collected from 7 private orthodontic practices as well as from the Graduate Orthodontic Clinic at the University of Michigan.	2	Same as Design.	2	The treated sample was compared with a sample of 30 subjects with untreated Class II malocclusions (control sample) selected from the University of Michigan Elementary and Secondary School Growth Study.
15	Baccetti et al 2000;118:404-13	11029736	3	Records from 105 patients with Class III malocclusion treated with a bonded rapid maxillary expander (RME) and facemask therapy were obtained from North American practitioners experienced in this type of treatment.	2	Records from 105 patients with Class III malocclusion treated with a bonded rapid maxillary expander (RME) and facemask therapy were obtained from North American practitioners experienced in this type of treatment.	4	Control samples with untreated Class III malocclusion were selected from the files of the Department of Orthodontics of the University of Florence.
16	Baccetti et al 2009	19524823	2 (?)	The conditions for patient enrollment, based on personal choice, could be assimilated to a random allocation of patients.	1	This investiga-tion was based on data collected during a series of pro-lective clinical trials on the dentoskeletal modifications produced	2	A sample of 28 subjects was selected from the University of Michigan Growth Study with the same dentoskeletal characteristics and skeletal maturational levels at T1 as the 2 treatment samples.

					in patients with Class II disharmony treated with different orthodontic or orthopedic approaches.		
17	Baik et al 2004	15014405	3	Thirty children (17 girls, 13 boys) with Class III malocclusions from the Department of Orthodontics, Yonsei University Dental Hospital, Seoul, Korea, treated with the FR III appliance, were selected as the treatment group.	2	Same as Design.	3	The control group consisted of 20 children (10 boys, 10 girls) of similar age (8.2 1.1 years old at the start of the study) who satisfied the criteria above (except for the last 2).
18	Barrett et al 2010	20889053	3	The treatment sample consisted of the cephalometric radiographs of 26 patients treated with the chincup.	2	The treatment sample consisted of the cephalometric radiographs of 26 patients treated with the chincup. All patients were treated with the same protocol by the same group of private practitioners	2 (?)	The cephalograms of the untreated patients were obtained from the University of Florence from clinic patients who initially refused treatment and sub-sequently returned seeking intervention and from the University of Michigan Growth Study
19	Baysal and Uysal 2013	21357655	1	Sixty Class II , division 1 , mandibular retrognathic patients were divided into three groups. Forty patients were randomly allocated to one of two functional appliance treatment groups.	1	Randomization was made at the start of the study with pre-prepared random number tables with block stratification on gender.	1	Control group compromised of 20 untreated subjects. Those were the patients who met the criteria but refused treatment with either appliance after initial records were taken.
20	Baysal and Uysal 2014	24663007	Same as 21357655					
21	Brunharo et al 2011	_R999983	1	This study was a prospective randomized clinical trial, …	1	The sample was randomly divided in two groups: the TB group (TBG) included 12 boys and 7 girls (mean age = 9 years and 6 months; sd = 10 months) and the Control group (CG)	1	Same as Act.
22	Cevidanes et al 2003	12695764	1	The Class II children were randomly allocated to 2 subgroups, treated and control, to avoid bias in the group comparison	1	Same as Design.	1	Same as Design.
23	Cevidanes et al 2010	20578848	EXCL	-	-	-	-	No untreated control
24	Cha and Ngan 2011	_R999984	Exclude	-	-	-	-	No untreated control
25	Chen et al 2012	21325335	2	A total of 39 growing children were selected from the patients who presented to the Orthodontic Department of Shanghai Jiao Tong University for Class III malocclusion consultation and treatment. The subjects were designated to either a treatment or control group.	1	Same as Design.	1	Same as Design.
26	Chiqueto et al 2013	23876947	2	Thus, the sample consisted of 44 young patients divided into two groups.	1	Same as Design.	2	The patients were selected from a sample provided by the Center for the Study of Growth, FOB-USP, where a group of children was X-rayed and checked annually by the Department of Orthodontics with the purpose of developing a longitudinal sample.
27	Courtney et al 1996	8659471	1	Forty-two children, who are 10 to 13 years old, with Class II, Division 1 malocclusions were matched in triads according to age and sex and randomly assigned to either the control, Harvold activator, or Frankel function regulator group.	1	Same as Design.	1	Same as Design.
28	de Almeida et al 2002	12045763	3	They were chosen from a parent sample of 50 based on best results obtained and compliance level from among the broader sample after 10 months in treatment. Initially,	2	Same as Design.	3	A control group, obtained from the files of the Longitudinal Growth Study of the University of Sao Paulo at Bauru,….
29	de Almeida et al 2005	16097222	2	This prospective clinical investigation evaluates…	1	Same as Design.	3	A control sample, derived from the files of the University of Sao Paulo (Bauru) Growth Study, comprised 30 subjects (15 boys, 15 girls; Table 1).
30	de Almeida et al 2008	18575306	2	Forty consecutive patients, selected prospectively, were treated for a Class II division 1 malocclusion….	1	Same as Design.	3	A control sample , derived from the files of the University of Bauru Growth Study, was comprised of 213 subjects (14 males, 14 females).
31	De Clerck et al 2010	21055597	2	...the treated sample was collected prospectively.	1	Success of therapy at the end of the observation period was not a determining factor for selection of patients, since the treated sample was collected prospectively.	4	A control group of 18 untreated subjects with dentoskeletal Class III malocclusion was obtained from the Department of Orthodontics of the University of Florence in Italy.
32	Deguchi and McNamara 1999	9971929	3	The records of the treated skeletal Class III subjects were obtained from the Department of Orthodontics, Matsumoto Dental Hospital, whereas the records of the untreated subjects were obtained from the files of a private clinic.	2	Same as Design.	4	Same as Design.
33	Dolce et al 2002	_R999988	1	Briefly, this was a prospective randomized clinical trial designed to examine the timing of Class II orthodontic treatment.	1	Same as Design.	1	Same as Design.

34	Ehmer et al 1999	10605275	1	the selected UNC patients were randomized and divided into 3 groups for the 15-month initial treatment phase (phase I): (-) UNC HG: early treatment group with combined headgear; (-) UNC Func: early treatment group with modified bionator; (-) UNC Cont: untreated control group for phase I of the trial; All patients selected for the WWU Münster group (Ger Func group) were treated with the Karwetzky Type I U-bow activator. The aim of establishing a non-randomized treatment group in Münster with identical selection criteria…..The prospective planning stipulated that preparation of , all initial documents…..	1	Same as Design.	1 (?)	To compare the skeletal treatment effects of the prospectively controlled initial 15-month treatment phase, using 2 different functional orthodontic appliances (USA UNC, Chapel Hill: modified Balters appliance; Germany WWU Münster: U-bow activator) and with reference to an untreated Class-II/1 control group (USA UNC: Chapel Hill).
35	Erdinç et al 1999	10474101	3	In this retrospective study, altogether 37 cases with posterior crossbites forming two treatment groups and one control group were treated at the Department of Orthodontics, Istanbul University, Faculty of Dental Medicine.	2	Same as Design.	3	Same as Design.
36	Falck and Zimmermann-Menzel 2008	18385956	3	In this retrospective clinical study…	2	Same as Design.	3	and 15 children served as a control group.
37	Flores-Mir 2009	19962605	2	This was a mixed study (treatment group of consecutively started patients and control group of a retrospective historical sample)	1	A prospective sample of 69 consecutive Class II patients treated..	2	To factor out the effects of growth over the treatment period, an untreated, age-matched Class II control group with skeletal and dental characteristics as similar as possible was obtained from the Burlington Growth Centre, Faculty of Dentistry, University of Toronto, in Ontario, Canada.
38	Forsberg 1981	6945995	2 (?)	Seventy-eight boys and girls with Class II Division 1 malocclusion were used in the study. Forty-seven of these patients were successfully treated with activators in accordance with Andresen's method.	1 (?)	Same as Design	4	The authors would like to thank Dr. Isaksson of Uppsala, Sweden for providing his longitudinal material of untreated Class II, division 1 cases.
39	Franchi et al 1999	10194289	Unclear	The treated group comprised 55 subjects with Class II malocclusion treated with the acrylic splint Herbst appliance followed by comprehensive edgewise therapy. The two control groups were one group of 30 subjects with untreated Class II malocclusion and another group of 33 subjects with Class I occlusion.	(?)	Same as Design.	2	The untreated Class II control group consisted of 30 subjects (15 females and 15 males) with untreated Class II malocclusions selected from the longitudinal records of the University of Michigan Elementary and Secondary School Growth Study.
40	Franchi et al 2004	15520688	3	The parent sample consisted of cephalometric records of 102 Class III subjects treated with RME/FM followed by comprehensive preadjusted edgewise therapy collected from 3 private orthodontic practices experienced in this treatment modality. The records of additional patients were obtained from the University of Michigan Graduate Orthodontic Clinic.	2	Same as Design.	4 (?)	Records for untreated Class III subjects were obtained from the orthodontic department at the University of Florence and the University of Michigan and 3 private orthodontic practices in Michigan.
41	Franchi et al 2011	21299410	3	Thirty-two Class II patients (mean age 12.761.2 years) were treated consecutively with the FRD protocol and compared with a matched sample of 27 untreated Class II subjects...	2	Same as Design.	2	A sample of 27 subjects was selected from the files of the University of Michigan Growth Study (12 subjects) and of the Denver Child Growth Study (15 subjects);
42	Gencer et al 2015	24913739	3	This retrospective study was carried out…	2	Same as Design.	3 (?)	The treatment groups were compared with an untreated control group of 15 patients (9 girls and 6 boys; mean age 5 10 years 5 months)
43	Geran et al 2006	16679203	2	The patients examined were part of a prospective clinical investigation...	1	The patients examined were part of a prospective clinical investigation, the Michigan Expansion Study, of mixed dentition patients who underwent RME in a private faculty practice.	2	Serial dental casts of 26 untreated subjects (18 male, 8 female) were obtained from the longitudinal records of the University of Michigan Elementary and Secondary School Growth Study
44	Ghislanzoni et al 2011	21299408	3	..subjects were selected according to the following inclusion criteria: ..., and follow-up observation at least 1 year after the end of comprehensive treatment with MARA and fixed appliances.	2	Same as Design.	2	The control ‘‘group’’ comprised data calculated on longitudinal series of 17 untreated Class II subjects selected from the University of Michigan and Denver Child Growth Studies.
45	Ghislanzoni et al 2013	22423185	2	The purpose of this prospective clinical trial, therefore, was to investigate the role of timing in the treatment of Class II malocclusion with MARA and fixed appliances...	1	Same as Design.	2	The control group consisted of data calculated on longitudinal series of untreated Class II subjects selected from the University of Michigan and Denver Child Growth Studies
46	Godoy et al 2011	21195256	1	The 99 children were randomly divided into 3 groups: QDH, expansion plate (EP), and untreated controls.	1	Same as Design.	1	Same as Design.
47	Gokalp and Kurt 2005	16097225	2 (?)	Whereas chin cup was applied on the treatment group, the control group was only observed without any intervening orthodontic treatment.	1 (?)	Same as Design.	1 (?)	Same as Design.
48	Goyenc 2004	14994882	2 (?)	Unclear	1	Unclear	1	To form the control group, lateral cephalograms were taken, with parental permission, from subjects who applied for but were not accepted for treatment at that time. Subsequently most received treatment.

49	Guimaraes 2013	22891750	2	Prospective study of dentoskeletal changes in…	1	Same as Design	3	The control group was selected from a longitudinal growth study sample from the files of the orthodontic department at Bauru Dental School, University of Sa˜o Paulo, Brazil,
50	Gunay et al 2011	22589581	2 (?)	A prospective study was carried out….{Our study was carried out on 54 lateral cephalometric radiographs???}	1	Same as Design.	3	To eliminate the effects of growth over the treatment period, an untreated, age-matched Class II control group with skeletal and dental characteristics as similar as possible was obtained from the Faculty of Dentistry Archieve, University of Yeditepe, in Istanbul, Turkey.
51	Handelman et al 2000	10833001	Exclude	-	-	-	-	No untreated control
52	Illing et al 1998	9825553	1	The material used in this prospective clinical study comprised... The first 58 patients who had been on the waiting list for the longest period were randomly allocated to one of three groups...	1	Same as Design.	1	The control group comprised 20 patients satisfying the above criteria, but who had more recently been placed on the department's functional appliance waiting list.
53	Isci et al 2010	20457582	Exclude	-	-	-	-	No untreated control
54	Isik et al 2005	16257988	Exclude	-	-	-	-	No untreated control
55	Jakobsone 2013	24326090	2	The sample considered in the present study was derived from a prospective sample of 180 patients described earlier	1	Same as Design	2	The control group consisted of 18 subjects (11 males, 7 females) who were selected from the longitudinal records of the University of Michigan Elementary and Secondary School Growth Study and the Denver Child Growth Study.
56	Jakobsson 1967	5229868	1	Within each triple it was decided by lot which patients were to receive treatment with either method and which was to serve as a control.	1	Same as Design.	1	Same as Design.
57	Janson et al 2003	12831221	3	Patients in the groups were retrospectively and randomly selected exclusively based on 4-premolar extraction treatment protocol.	2	Same as Design.	3	The control group (group 4) consisted of subjects with untreated malocclusion.
58	Jena et al 2006	17110256	2 (?)	Girls with a history of orthodontic treatment, an anterior open bite, a severe proclination of the maxillary and mandibular teeth, or a systemic disease affecting growth were not considered for this study.	1 (?)	Same as Design.	1 (?)	Ten subjects constituted the control group; they received no treatment but were followed until the end of the study.
59	Kajiyama et al 2000	11094369	2 (?)	Twenty-nine patients (11 boys, 18 girls) with Class III malocclusion (treatment group) were actively treated with the MPBA.	1 (?)	Same as Design.	3	The control group consisted of 25 children (10 boys, 15 girls) with Class III malocclusion who received no active treatment.
60	Kajiyama et al 2004	15224055	3	They were selected from approximately 5000 patients in the Orthodontic Clinic of the Kyushu University Dental Hospital on the basis of the following criteria: ... (5) no previous orthodontic treatment.	2	Same as Design.	3	The untreated children served as controls after informed consent was obtained from their parents.
61	Kalavritinos et al 2005	15827701	3	The aim of this retrospective clinical study was…	2	Same as Design.	2 (?)	The records of the untreated Class III subjects were obtained from the Department of Orthodontics at the University of Florence, the University of Michigan Elementary and Secondary School Growth Study, and three private orthodontic practices in Michigan (USA)
62	Karacay et al 2006	16808575	1	The patients were divided into three equal groups randomly.	1	Same as Design.	1	Same as Design.
63	Kilicoglu and Kirlic 1998	9563362	1	The patients were divided randomly into the treatment (n = 16) and control (n = 10) groups.	1	Same as Design.	1	Same as Design.
64	Kucukkeles et al 2007	17465652	3	The sample consisted of the records from 45 growing patients (22 boys, 23 girls) exhibiting skeletal Class II malocclusion characterized by mandibular retrognathism. Twenty-five patients (12 boys, 13 girls) with a mean age of 11.83 years were treated with the Jasper Jumper appliance followed by standard edgewise mechanics. A control group was formed by the records of 20 skeletal Class II patients with a mean age of 11.3 years who were observed for 6 months before orthodontic treatment...	2	Same as Design.	3	Same as Design.
65	Ladner and Muhl 1995	7625394	Exclude	-	-	-	-	No untreated control
66	Latkauskiene 2012	_R999987	2	The aim of this prospective study was…	1	Study subjects were selected from the patients referred to Kaunas Ortodontijos Centras clinic for orthodontic treatment.	2	The control group consisted of 18 subjects (11 males, 7 females) who were selected from the longitudinal records of the University of Michigan Elementary and Secondary School Growth Study and Denver Growth Study.
67	Lee et al 2010	20482355	Exclude	-	-	-	-	No untreated control
68	Levin et al 2008	18929269	3	The aim of this retrospective controlled investigation…	2	Selected subjects were identified as having satisfactory cooperation during treatment and having achieved adequate anterior oral seal at T3.	4	The subjects for these groups were derived from records at the University of Florence and the University of Michigan.

69	Lin et al 2007	17561473	3	Twenty children (10 boys and 10 girls) with Class III malocclusion consecutively treated with OMA appliance of Mx protraction combined with chincup traction were selected as the treated group.	2	Same as Design.	3	Records of the untreated Class III subjects were obtained from the growth study material which had been collected as a control group in this study.
70	Lund and Sandler 1998	9457025	2	This prospective controlled study investigated the net effects of the Twin Block functional appliance taking into account the effects of normal growth in an untreated control group	1	Same as Design.	1	the control group consisted of 27 subjects (13 male and 14 female) who had been referred for orthodontic treatment but then placed on the waiting list for functional appliance treatment.
71	Mandall et al 2010	20805344	1	The patient was then randomly allocated to the protraction facemask group (PFG) or control/no treatment group (CG).	1	Same as Design.	1	Same as Design.
72	Martina et al 2013	23323608	1	Enrolled patients were allocated to either a treatment (BJA) or control (CTR) group by balanced block randomization using gender as a stratifying factor.	1	Same as Design.	1	Same as Design.
73	Masucci et al 2011	21967936	2	The study included Class III subjects treated consecutively with the orthopedic protocol in a prospective design…	1	Same as Design.	3 (?)	All subjects in the control groups had been followed longitudinally at the Department of Orthodontics of the University of Florence
74	Masucci et al 2014	25041370	3	The aim of the present retrospective study…	2	To be included in this study, all treated patients had to present with the following dentoskeletal features…	2 (?)	These subjects were selected from the files of the Department of Orthodontics of the University of Florence and from the AAOF Craniofacial Growth Legacy Collection (http://www.aaoflegacycollection.org, Bolton–Brush Growth Study and Michigan Growth Study).
75	McNamara et al 2003	12940553	2	The treated sample analyzed in this study (112 subjects, 61 females and 51 males) was part of a longterm prospective study on consecutively treated patients who had undergone Haas-type RME and nonextraction edgewise appliance therapy in a single orthodontic practice...	1	Same as Design.	2	The records were derived from both the University of Michigan Elementary and Secondary School Growth Study12 and the University of Groningen Growth Study.
76	Mills and McCulloch 1998	9674675	3	Pretreatment and posttreatment cephalometric records of 28 consecutively treated patients with Class II malocclusions were evaluated and compared with an age- and sex-matched sample of untreated Class II control subjects.	2	Same as Design.	2	Records for a control group of 28 untreated persons with Class II malocclusions were obtained from the Burlington Growth Centre at the University of Toronto.
77	Moro et al 2009	19216611	2	This prospective cephalometric study was conducted…	1	Same as Design.	3	The untreated Class II malocclusion control group consisted of 26 subjects (15 male and 11 female; mean initial age, 9.8 years; range, 9 to 11 years) from the longitudinal records of the same department.
78	Morris et al 1998	9926634	1	A prospective clinical study with a random allocation of 47 patients to three different functional appliance groups	1	Same as Design.	1	From Illing 1998.
79	Nalbantgil et al 2005	15898385	(?)	Our study was carried out on 75 lateral cephalometric films, 15 of which were taken off the treatment group before the leveling stage.	(?)	Same as Design.	(?)	Same as Design.
80	Nelson et al 1993	8338068	1	...subjects were then grouped in triads, and one subject in each triad was randomly assigned to either the control, the Friinkel function regulator (FFR), or the Harvold "activator (HA) group (Fig. 1)….	1	Same as Design.	1	Same as Design.
81	Ngan et al 1996	8540481	Exclude	-	-	-	-	No untreated control
82	O'Brien et al 2003	12970656	1	After initial recording of patient data, each patient was randomized to receive treatment with a Twin-block appliance or to have treatment delayed for at least 15 months.	1	Same as Design.	1	Same as Design.
83	O'Grady et al 2006	16905065	2	The patients examined were part of the MES, a prospective clinical investigation of mixed-dentition patients who had undergone RME.	1	Same as Design.	2	Serial dental casts of 16 untreated subjects (9 male, 7 female) were obtained from the longitudinal records of trhe University of Michigan Elementary and Secondary School Growth Study as the CTRL
84	Oztoprak et al 2012	22904659	2	The purpose of this clinical prospective study was to compare the dentofacial changes produced by the Sabbagh Universal Spring (SUS²) and Forsus FRD appliances...	1	Same as Design.	3	To eliminate the effects of growth over the treatment period, an untreated, age-matched Class II control group with skeletal and dental characteristics as similar as possible was obtained from the Faculty of Dentistry Archieve, University of Yeditepe, in department of orthodontics.
85	Pancherz 1982	6961781	2 (?)	The control subjects were followed on a parallel basis with the treated subjects during a time period of 6 months...	1	Same as Design.	1	Same as Design.
86	Pangrazio et al 2012	22432591	3	This retrospective cephalometric study examined 30 consecutively treated patients...	2	Same as Design.	2	The control group was composed of 21 subjects from the Michigan Growth Study who conformed to the inclusion criteria.
87	Pangrazio-Kulbersh et al 2003	12637901	3 (?)	The study involved the cephalometric evaluation of 30 patients treated with the MARA from 1 private practice.	2	Same as Design.	2	The experimental MARA subjects were compared with 21 Class II control subjects (13 girls and 8 boys) from the Michigan Elementary and Secondary School Growth Study
88	Petren and Bondemark 2008	18538237	1	The patients were randomized into 4 groups...4 opaque envelopes were prepared with 20 sealed notes in each (5 notes for each group).	1	Same as Design.	1	Same as Design.

89	Petren et al 2011	21195260	1 (?)	…, we used randomized controlled trial methodology to follow them for 3 years posttreatment.	1	Same as Design.	1 (?)	The normal control group was recruited from the Institute for Postgraduate Dental Education, Jonkoping, Sweden. These subjects had normal sagittal occlusion and no crossbite or other malocclusion traits, and were matched for age and dental age to the treated subjects.
90	Phatouros and Goonewardene 2008	18617111	3	The purpose of this retrospective study was to estimatethe areachange...	2	Same as Design.	3	Same as Design.
91	Phelan et al 2012	22640678	2	This prospective clinical study was based on the records of 34 consecutively treated patients...	1	Same as Design.	2 (?)	The control subjects were derived from the University of Michigan Elementary and Secondary School Study and the University of Florence in Italy.
92	Quintao et al 2006	16113035	2	The sample comprised 38 subjects, prospectively recruited, from those awaiting treatment at the Orthodontic Post…	1	Same as Design.	1	Nineteen patients were treated with a TB functional appliance and the other 19 formed the control group.
93	Sandikcioglu and Hazar 1997	9082855	Exclude	-	-	-	-	No untreated control
94	Sar et al 2011	21536207	2	All subjects and parents were informed of the experimental protocols and signed an informed consent form that was previously approved by the ethics committee of the University of Baskent. The selected patients were divided into 3 groups of 15 patients each.	1	Same as Design.	1	Same as Design.
95	Shundo et al 2012	21674183	3	The subjects in the treatment and control groups were selected retrospectively...	2	Same as Design.	3	Observation of the control group patients was made once in 2 or 3 months, without any orthodontic appliances during the T0–T1 period.
96	Siara-Olds et al 2010	19852635	3	In this retrospective long-term investigation, ….	2	Same as Design.	2	The untreated control group comprised 21 children from the Michigan and Denver Growth Study samples.
97	Sidlauskas 2005	15947523	3	The treatment group consisted of 34 cases treated in the Clinic of Orthodontics, Kaunas University of Medicine.	2	Same as Design.	2	…,a comparison was made with longitudinal growth records of persons with excellent occlusion – Bolton standards (14).
98	Silvestrini-Biavati 2012	23270288	2	A prospective controlled study	1	Same as Design	2	As control group, 20 causasian untreated subjects mean data were used (14 males, 6 females, mean age 9y 1 m), from "Growth Study University of Michigan" and "Denver Child Growth Study"
99	Tortop 2007	17920499	3 (?)	In this study, we aimed to compare facemask treatment results between expansion and nonexpansion groups and between treated groups and a control group; all groups were matched by age and sagittal skeletal relationship. The material of this study consisted of the lateral cephalograms of 42 children with...	2	Same as Design	3	A retrospective control group of 14 children (7 girls, 7 boys; mean age, 10 years 4 months) was observed without treatment for 10 months.
100	Toth and McNamara 1999	10587592	3	This retrospective cephalometric study compares…	2	Same as Design.	2	Changes during treatment were compared with the cephalometric records of 40 untreated children from The University of Michigan Elementary and Secondary School Growth Study (UMGS)
101	Trenouth 2000	10629520	3	Any retrospective study is likely to introduce bias by producing an inflated view of treatment outcome. Only successfully treated cases were included in the study because as with most retrospective studies the patients who failed to complete treatment did not have a final cephalometric radiograph.	2	Same as Design	2 (?)	The normative data published by Bhatia and Leighton33 derived from London school children was chosen because of its nearest geographic proximity.
102	Tulloch et al 1997	9109584	1	In phase 1 of the trial, each child was randomly assigned by using a stratified block randomization, with gender as the stratification factor, to one of three groups, headgear, functional appliance, or observation only.	1	Same as Design.	1	Same as Design.
103	Tulloch et al 2004	15179390	1	During the first phase of the trial, the children were randomly assigned, by using block randomization with sex as the stratification factor, to treatment starting in the mixed dentition (either combination headgear or a modified bionator) or to observation only.	1	Same as Design.	1	Same as Design.
104	Tümer and Gültan 1999	10511676	2	The subjects of the treatment groups were split into 2 groups, each composed of 13 individuals.	1	Same as Design.	1	The subjects of the control group were followed for 14 months without any intervention.
105	Tuncer et al 2009	19522895	3	The lateral cephalometric radiographs of all patients were obtained retrospectively from the files of Class III subjects according to the following criteria…	2	Same as Design.	3	Eighteen untreated control subjects (eight girls, 10 boys, mean chronological age 9.89 +-1.55 years) were matched according to skeletal developmental stage (P = 0.128), and displayed Class III skeletal relationship with mandibular prognathism.
106	Ucem et al 2004	15592214	3 (?)	Data were based on the pretreatment and posttreatment lateral cephalograms of 28 subjects with dental Class III malocclusions and anterior crossbites.	2	Same as Design.	3	Same as Design.
107	Ulgen and Firatli 1994	8198080	1	The patients were divided randomly into treatment and control groups.	1	Same as Design.	1	Same as Design.

108	Usumez et al 2004	15529493	3	Ten male and 10 female patients, treated between 2000 and 2002, were selected as the treatment group.	2	Same as Design.	3	The remaining samples formed the untreated control group to eliminate possible growth effects. The subjects in the control group were informed about orthodontic treatment but refused treatment.
109	Uyanlar et al 2014	_R999986	2 (?)	This prospective study consisted of 27 patients.. Our study was carried out on 54 lateral cephalometric films that were taken before placement and after removal of the SUS² appliance in the treatment group and at the beginning and six months after in the control group.	1	Same as Design.	1	Same as Design.
110	VanLaecken et al 2006	17110255	3	This retrospective study was performed with..	2	Same as Design.	2	The control group consisted of serial cephalometric radiographs of 32 subjects (16 boys, 16 girls) with no history of orthodontic treatment from the Bolton-Brush Study.
111	Varlik et al 2008	18281262	1	Fifty Class II division 1 children…., and randomly assigned to either the TB or activator treatment group for first-phase orthodontic treatment.	1	Same as Design.	1	These patients were placed on the department's waiting list for one-phase orthodontic treatment.
112	Vaughn et al 2005	16168327	1	The purpose of this controlled randomized clinical trial…	1	Same as Design.	1	Group C was the control or observation group.
113	Waheed-Ul-Hameed 2002	_R999982	3	Two groups were selected; the first group of 10 patients was treated with the Frankel appliance and the other 10 patients taken as a control group.	2	Same as Design.	3	The study material comprised 20 patients from our clinical intake
114	Yuksel et al 2001	11668875	2	The sample consisted of 34 children with skeletal and dental Class III malocclusions, with an age range between 8 years 2 months and 14 years 3 months. None of the subjects had a history of previous orthodontic treatment.	1	Same as Design.	1	A control group consisting of 17 children with a mean age of 9 years 5 months (with an age range of 8 years 5 months–10 years 2 months) was formed matched to the early treatment group. The observation period was 9 months. For ethical reasons it was not possible to find a control for the late treatment group.

STUDIES IDENTIFIED FROM THE SEARCH UPDATE

1	Altug 2004	_R999981	3 (?)	From translation	2	From translation	3	Translation:"...group of 17 selected individuals from the archives..."
2	Faltin 2003	12828429	3	The cephalometric records of 30 class-II malocclusion patients consecutively treated with the Bionator were collected from a single orthodontic practice where this type of therapy was used.	2	Same as Design	2	The treated sample was compared with a sample of 21 subjects with untreated class-II malocclusions (control sample) selected from the University of Michigan Elementary and Secondary School Growth Study
3	Fernandes 2007	_R999980	1	"Cinqüenta e oito pacientes foram selecionados e distribuídos aleatoriamente nos três grupos de acompanhamento da pesquisa." (p.20)	1	Same as Design	1	Same as Design
4	Firouz 1992	1510043	2	"In the present study a prospective cephalometric investigation…" (p.1)	1	Same as Design	1	"Twelve patients received headgear therapy for 6 months, and the remaining patients served as controls."
5	Giuntini 2015	25786056	3	The aim of the present retrospective controlled clinical study….	2	Same as Design	2	The control group consisted of 27 subjects (13 females and 14 males) with untreated Class II malocclusion, the records of whom were selected from the files of the University of Michigan Growth Study (11 subjects), the Denver Child Growth Study (9 subjects), and the Bolton-Brush Growth Study (7 subjects).
6	Henriques 2004	_R999979	3 (?)	"A amostra constituiu-se de 150 telerradiografias em norma lateral, de 75 jovens brasileiros de ambos os gêneros provenientes do acervo da Disciplina de Ortodontia da Faculdade de Odontologia de Bauru, Universidade de São Paulo." (p.86)	2	Same as Design	3	"Selecionou-se esta amostra a partir de um grupo de jovens que foi anualmente radiografado e controlado pela Disciplina de Ortodontia da FOB-USP com o fim de obter uma amostra longitudinal de jovens, desde a dentadura mista até a permanente." (p.87)
7	Jakobsson 1967	5229868	2	"Within each triple it was decided by lot which patients were to receive treatment with either method and which was to serve as a control."	1	Same as Design	1	Same as Design
8	Keeling 1998	9457018	1	"In this study we examined anteroposterior cephalometric changes in children enrolled in a randomized controlled trial of early treatment for Class II malocclusion" (p.17)	1	Same as Design	1	Same as Design
9	Kocadereli 1992	_R999978	3 (?)	From translation	2	From translation	3	No description
10	Mäntysaari 2004	14994883	1	"...a report of a 2 year randomized study" (p.1)	1	Same as Design	1	Same as Design
11	Nahas 2003	_R999977	2	"Como todos os pacientes de ambos os grupos experimentais foram tratados de modo específico, com o objetivo de estudá-los posteriormente, este estudo se caracteriza como prospectivo,..."	1	Same as Design	2	"Todos os pacientes que compõem os grupos controles são de origem caucasiana, canadenses, originários do arquivo de documentações Burlington Growth Centre, localizado na Faculdade de Odontologia da Universidade de Toronto, Canadá."
12	Ölmez 1994	_R999976	2 (?)	From translation	1	From translation	1	No description
13	Paulin 2004	_R999975	2	"A amostra prospectiva, analisada longitudinalmente, considerada grupo experimental…"	1	Same as Design	2	"A amostra retrospectiva, considerada grupo controle e analisada longitudinalmente, foi selecionada junto aos arquivos do Burlington Growth Center,…"
14	Perillo 2013	24325832	3	This retrospective controlled study aimed at evaluating…	2	Same as Design	3	Subjects who refused to be treated at the initial visit but re-presented later were included in the control group whenever a second set of diagnostic recording was available.
15	Tosun 1991	_R999974	2 (?)	From translation: "that individuals were included in the study believed that cooperation could be made."	1	Same as Design	3	From translation: "The control group A. u. Faculty of Dentistry, Department of Orthodontics selected i2 girl from the archive,…"

16	Tulloch 1997	91095843	1	"In this controlled clinical trial, patients in the mixed dentition with overjet _> 7 mm were randomly assigned to either" (p.1)	1	Same as Design	1	Same as Design
17	Ulgen 1991	_R999973	3 (?)	From translation	2	From translation	3	No description
18	Zhang 2010	_R999972	3 (?)	From translation	2	From translation	3	No description

Supplementary Table 5. Details of the included component trials with historical control groups from longitudinal growth studies.

Nr	Trial	PMID	Growth study used
1	Angelieri 2014	23736378	Michigan GS & Denver GS
2	Al-Jewair 2012	22214390	Michigan GS
3	Arman 2006	16731542	Unclear
4	Arman 2004	15673133	Unclear
5	Baccetti 2000	10935956	Michigan GS
6	Baccetti 2009	19524823	Michigan GS
7	Barrett 2010	20889053	Michigan GS & University of Florence archives
8	Faltin 2003	12828429	Michigan GS
9	Flores-Mir 2009	19962605	Burlington GS
10	Franchi 1999	10194289	Michigan GS
11	Franchi 2011	21299410	Michigan GS & Denver GS
12	Geran 2006	16679203	Michigan GS
13	Ghislanzoni 2011	21299408	Michigan GS & Denver GS
14	Ghislanzoni 2013	22423185	Michigan GS & Denver GS
15	Giuntini 2015	25786056	Michigan, Denver GS & Bolton-Brush GS
16	Jakobsone 2013	24326090	Michigan GS & Denver GS
17	Kalavritinos 2005	15827701	Michigan GS, University of Florence archives; archives of three private practices
18	Latkauskiene 2012	_R999987	Michigan GS & Denver GS
19	Masucci 2014	25041370	Bolton-Brush GS, Michigan GS & University of Florence archives
20	McNamara 2003	12940553	Michigan GS & University of Groningen GS
21	Mills 1998	9674675	Burlington GS
22	O'Grady 2006	16905065	Michigan GS
23	Pangrazio 2012	22432591	Michigan GS
24	Pangrazio-Kulbersh 2003	12637901	Michigan GS
25	Phelan 2012	22640678	Michigan GS & University of Florence archives
26	Siara-Olds 2010	19852635	Michigan GS & Denver GS
27	Sidlauskas 2005	15947523	Bolton-Brush GS
28	Silvestrini-Biavati 2012	23270288	Michigan GS & Denver GS
29	Toth 1999	10587592	Michigan GS
30	Trenouth 2000	10629520	King's College London GS
31	VanLaecken 2006	17110255	Bolton-Brush GS

	Growth study	Frequency	Details
1	Michigan GS	24	University of Michigan – Ann Arbor, Michigan, USA
2	Denver GS	9	University of Oklahoma – Oklahoma City, Oklahoma, USA
3	Bolton-Brush GS	4	Case Western Reserve University – Cleveland, Ohio
4	Burlington GS	2	University of Toronto – Toronto, Ontario, Canada
5	University of Groningen GS	1	University of Groningen – Groningen, The Netherlands
6	King's College London GS	1	King's College London – London, UK

GS, growth study; USA, United States of America; UK, United Kingdom.

Supplementary 6. Detail of the extracted meta-analyses and their subsequent inclusion/exclusion in the present study.

MA	PMIDs	Problem	Intervention	Outcome	Added trials	Total trials	Included
1	25679781	Class III	Chincup	SNA	-	5	Yes
2	25679781; 20936970	Class III	Chincup	SNB	-	8	Yes
3	25679781; 20936970	Class III	Chincup	ANB	-	8	Yes
4	25679781	Class III	Chincup	WITS	-	3	Yes
5	25085296	Class III	Fränkel appliance	SNA	-	5	Yes
6	25085296	Class III	Fränkel appliance	SNB	-	5	Yes
7	25085296	Class III	Fränkel appliance	ANB	-	5	Yes
8	25085296	Class III	Fränkel appliance	Overjet	-	4	Yes
9	25982454; 26068221	Class III	Maxillary protraction	SNA	2	7	Yes
10	25982454; 26068221	Class III	Maxillary protraction	SNB	2	7	Yes
11	25982454; 26068221	Class III	Maxillary protraction	ANB	2	7	Yes
12	25982454	Class III	Maxillary protraction	A-point horizontal	2	4	Yes
13	25982454; 26068221	Class III	Maxillary protraction & expansion	SNA	2	9	Yes
14	25982454; 26068221	Class III	Maxillary protraction & expansion	SNB	2	9	Yes
15	25982454; 26068221	Class III	Maxillary protraction & expansion	ANB	2	9	Yes
16	23828862	Transverse discrepancy	Maxillary expansion	Maxillary intermolar width	-	8	Yes
17	23828862	Transverse discrepancy	Maxillary expansion	Maxillary intercanine width	-	7	Yes
18	23828862	Transverse discrepancy	Maxillary expansion	Maxillary interpremolar width	-	4	Yes
19	25995359; 25398303; 25052373	Class II	Functional appliances	SNA	7	29	Yes
20	25995359; 25398303; 25052373	Class II	Functional appliances	SNB	7	29	Yes
21	25995359; 25398303	Class II	Functional appliances	ANB	7	25	Yes
22	25188504; 25181253	Class II	Functional appliances	Total mandibular length	-	14	Yes
23	25188504	Class II	Functional appliances	Composite mandibular length	-	4	Yes
24	25052373	Class II	Functional appliances	Co-Gn	5	8	Yes
25	25181253	Class II	Functional appliances	Mandibular corpus length	2	6	Yes
26	25181253	Class II	Functional appliances	Mandibular ramus length	2	7	Yes
27	25679781	Class III	Chincup	Co-Gn	-	3	No
28	25679781	Class III	Chincup	Co-Go	-	*	No
29	25679781	Class III	Chincup	Gonial angle	-	4	No
30	25679781	Class III	Chincup	N-Me	-	*	No
31	25679781	Class III	Chincup	UFH	-	*	No
32	25679781	Class III	Chincup	LAFH	-	*	No
33	25679781	Class III	Chincup	SN-ML	-	4	No
34	25679781	Class III	Chincup	Overjet	-	*	No
35	25679781	Class III	Chincup	Overbite	-	*	No
36	25085296	Class III	Fränkel appliance	MPA	-	4	No
37	22458766	Class III	Skeletal-anchored maxillary protraction	A-VR	-	2	No
38	25982454	Class III	Maxillary protraction	MPA	2	4	No
39	25982454	Class III	Maxillary protraction	PP	2	4	No
40	25982454	Class III	Maxillary protraction	U1 angulation	1	3	No
41	26068221	Class III	Maxillary protraction	ANS-Me	1	4	No
42	26068221	Class III	Maxillary protraction	SN/Co-Gn	-	4	No
43	25982454	Class III	Maxillary protraction & expansion	MPA	3	6	No

44	26068221	Class III	Maxillary protraction & expansion	SN/Co-Gn	-	3	No
45	25982454	Class III	Maxillary protraction & expansion	PP	3	6	No
46	26068221	Class III	Maxillary protraction & expansion	ANS-Me	2	6	No
47	25982454	Class III	Maxillary protraction & expansion	U1 angulation	-	3	No
48	23828862	Transverse discrepancy	Maxillary expansion	Mandibulary intermolar width	-	7	No
49	25995359; 25398303	Class II	Functional appliances	SNPg	1	4	No
50	25995359; 25398303	Class II	Functional appliances	NAPg	1	8	No
51	25398303	Class II	Functional appliances	NSBa	1	3	No
52	25995359; 25398303	Class II	Functional appliances	SN-ML	4	19	No
53	25398303	Class II	Functional appliances	FH-ML	1	6	No
54	25398303	Class II	Functional appliances	SN-SGn	-	2	No
55	25995359; 25398303	Class II	Functional appliances	NL-ML	1	6	No
56	25995359; 25398303	Class II	Functional appliances	SN-NL	2	14	No
57	25398303	Class II	Functional appliances	FH-NL	1	3	No
58	25995359; 25398303	Class II	Functional appliances	SN-OP	1	7	No
59	25398303	Class II	Functional appliances	ML-OP	-	1	No
60	25995359; 25398303	Class II	Functional appliances	ArGoMe	2	6	No
61	25995359; 25398303	Class II	Functional appliances	1s-SN	1	10	No
62	25995359; 25398303; 25052373	Class II	Functional appliances	1s-NL	5	12	No
63	25995359; 25398303; 25052373	Class II	Functional appliances	1i-ML	6	27	No
64	25995359; 25398303	Class II	Functional appliances	1s-1i	1	9	No
65	25995359; 25398303	Class II	Functional appliances	1s-NA	2	8	No
66	25995359; 25398303	Class II	Functional appliances	1i-NB	2	8	No
67	25398303	Class II	Functional appliances	6s-NL	1	4	No
68	25398303	Class II	Functional appliances	6i-ML	1	3	No
69	25995359; 25398303	Class II	Functional appliances	N'SnPg'	-	3	No
70	25995359; 25398303	Class II	Functional appliances	Nasolabial angle	-	9	No
71	25995359; 25398303	Class II	Functional appliances	Mentolabial angle	-	3	No
72	25995359; 25398303	Class II	Functional appliances	H angle	-	6	No
73	25398303	Class II	Functional appliances	Z angle	-	2	No
74	25995359	Class II	Functional appliances	SGo:NMe	-	4	No
75	25995359	Class II	Functional appliances	CoGoMe	-	1	No
76	25995359	Class II	Functional appliances	Y axis	-	2	No
77	25995359	Class II	Functional appliances	1i-VL	-	3	No
78	25995359	Class II	Functional appliances	ANSMe:NMe	-	3	No
79	25995359	Class II	Functional appliances	Gonial ratio	-	3	No
80	25995359	Class II	Functional appliances	S-Ar/Ar-Go	-	2	No
81	25052373	Class II	Functional appliances	LAFH	-	3	No
META-ANALYSES ADDED FROM THE SEARCH UPDATE							
1	_R999971	Class II	Headgear	SNA	-	12	Yes
2	_R999971	Class II	Headgear	SN-NL & FH-NL	-	12	No
3	_R999971	Class II	Headgear	Co-A & Nperp-A	-	8	Yes
4	_R999971	Class II	Headgear	Nasolabial angle	-	4	No

*after pooling of multiple trial arms from the same trial, less than two studies were included.

Supplementary Table 7. Results for the effect of the confounders on the trial results (expressed as intervention minus control with the standardized mean difference).

Comparison (Cat1 vs Cat2)	MAs	Trials	Trials (Cat1/Cat2)	Effect on trial results			Heterogeneity	
				ΔSMD (95% CI)	P-value	95% predictive interval	I^2 (95% interval)	τ^2
Retrospective vs prospective interventional group	13	171	122/48[$]	0.49 (0.19, 0.79)	***	-0.16, 1.14	26% (0%, 61%)	0.06
Trial sample size (per 10 patient increase)	13	171	-	-0.01 (-0.05, 0.04)	-	-0.09, 0.07	13% (0%, 55%)	0

Cat, category; MA, meta-analysis; ΔSMD, difference in standardized mean differences (due to recoding, negative values indicate smaller treatment effect for studies in the first category); CI, confidence interval.

[$]One trial with unclear interventional group excluded

*P<0.05

** P<0.01

***P<0.001

Supplement. Supplementary information on this systematic review

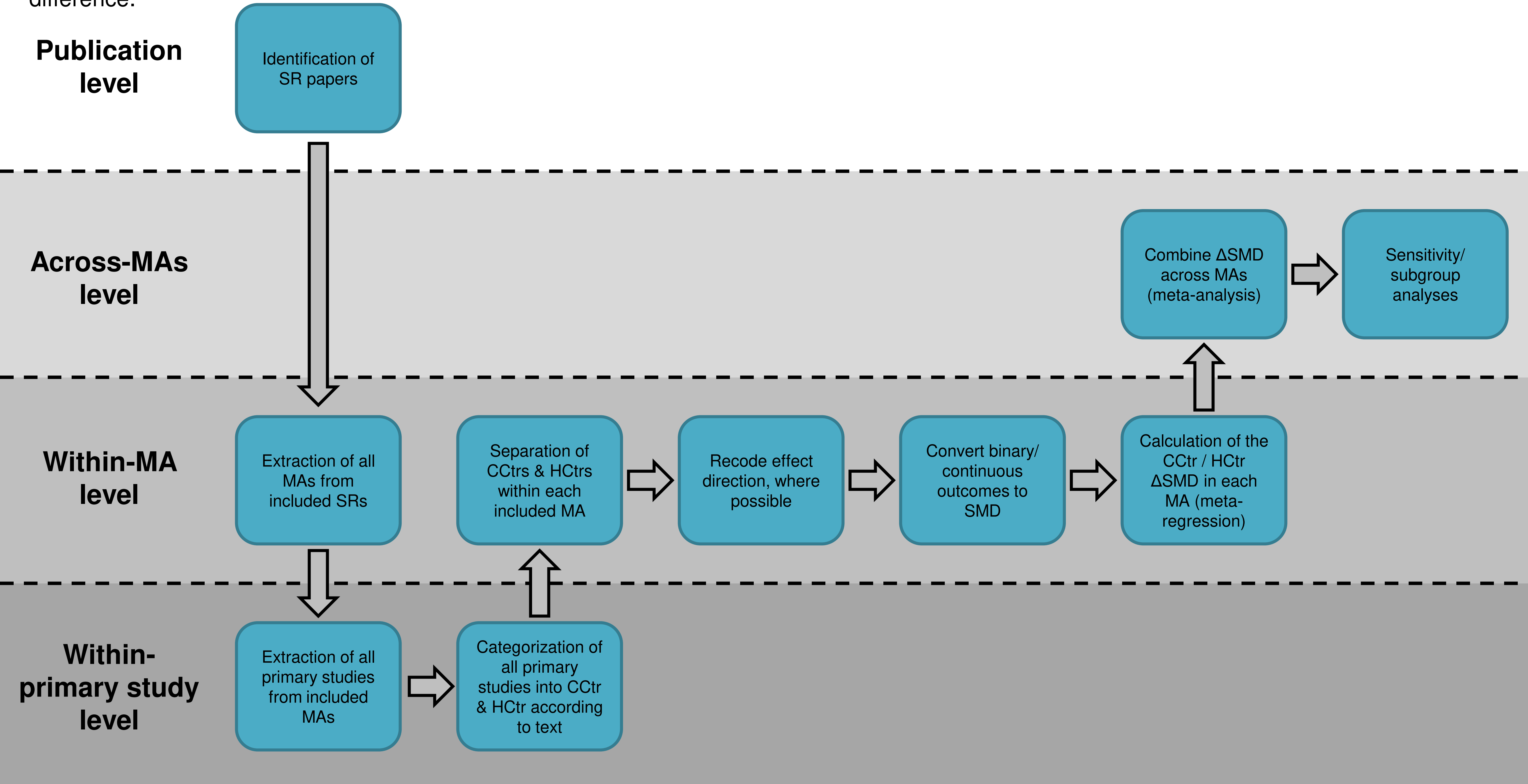
Author contributions

SNP conceived idea and wrote the protocol; SNP, VK, and AJ revised the protocol; SNP performed the literature searches, extracted search hits, and did study selection from title; SNP, VK did study selection by abstract and full-text, did manual searches to augment the electronic ones, and performed did data extraction: SNP, VK. AJ resolved conflicts at any stage; SNP handled communications with authors for extra data, did the statistical analyses, and wrote the first draft; SNP, VK, and AJ interpreted the analyses and revised the draft; SNP submitted the manuscript and is responsible for correspondence and for the accuracy of the data.

Post hoc changes from the protocol

- No kappa statistic was used to compare duplicate procedures between the two assessors, as was planned, as after piloting almost perfect agreement with minor differences was found.
- It was decided to adjust the effect of the control group's nature for the nature of the intervention group via multivariable meta-regression, which was not planned *a priori*.
- A number of subgroup analyses (binary versus continuous outcomes; subjective versus objective outcomes) could not be performed.
- Originally it was planned to perform a sensitivity analysis by including only meta-analyses with 10 studies. However, the choice of 10 studies per meta-analyses was judged as arbitrary. Instead, a sensitivity analysis was conducted with the most precise 50% of the included meta-analyses (i.e. having the smallest standard error).
- During manuscript preparation, a method was introduced to calculate sample size for meta-epidemiological studies. This was adopted *post hoc* to check the power of this study.

Supplementary Figure 1. Graph explaining the study's procedures regarding the meta-epidemiological comparison between trials with concurrent control groups (CCtrs) and trials with historical control groups (HCtrs). SR, systematic review; MA, meta-analysis; CCtr, trial with concurrent control group; HCtr, trial with historical control group; SMD, standardized mean difference; ΔSMD, difference in standardized mean difference.



Supplementary Figure 2. Contour enhanced funnel plots for the assessment of reporting biases in the comparison of historical vs concurrent controls (upper) and growth study vs clinical archive historical control (lower).